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DIAGNOSIS AND MANAGEMENT OF PYELONEPHRITIS

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OF the four common nephropathies, glomerulonephritis, nephrosclerosis, intercapillary glomerulosclerosis and pyelonephritis, at present only pyelonephritis, the most familiar of these, offers the possibility of arrest or cure. It has been strangely neglected, possibly because it is a nosologic stepchild, half surgical and half medical. Volhard and Fahr in 1914[1] did not list it among medical diseases of the kidney nor did Addis in 1925.[2] Apart from the pediatric, obstetric and urologic aspects, little of general interest was written about it until 1939 when Weiss and Parker[3] explored its relationship to hypertensive disease. In 1948 Raaschau[4] of Copenhagen published an excellent monograph on the subject with extensive pathologic and clinical studies. His most striking observation concerns its incidence. Among 3607 routine autopsies he found histopathologic evidence of pyelonephritis in 5.6 per cent. One half of these persons had died of renal failure but in only 1 out of 6 was the condition recognized ante mortem. Undoubtedly, if a disease is both common and remediable, its diagnosis and treatment are of general interest.

Etiology and Pathology

The most common organisms in pyelonephritis are colon bacilli and hemolytic streptococci. In some cases the infection is secondary to lesions which prevent free urinary drainage. In this group surgical correction of the causes of urinary stasis usually permits eradication of infection. Among the remaining patients the process is primary with no demonstrable anatomic abnormality. The organisms apparently reach the kidney substance through the blood stream. The pelvis and lower urinary tract become involved by contamination with infected urine.

Following infection, a focal or diffuse inflammatory process develops which involves all types of renal tissue, glomerular, tubular, interstitial and vascular. If the condition is unchecked the result is progressive scar formation with destruction of kidney substance which leads to hyalinization of the glomeruli and eventual atrophic kidney. The arterioles show proliferative endarteritis which Weiss and Parker suggest may account for the arterial hypertension occasionally noted in patients with pyelonephritis. The end stage closely resembles, and is even indistinguishable from terminal glomerulonephritis.

Diagnosis

In the group of patients with surgical lesions of the urinary tract, history, urinalysis and cultures, cystoscopy and pyelography establish diagnosis with little difficulty. Patients with primary pyelonephritis who give a history of recurrent chills and fever with dysuria accompanied by tenderness or pain in the kidney region will have pyuria and bacilluria during active phases. However, some are free of symptoms until they reach advanced stages of renal insufficiency and exhibit the evidences of early uremia and anemia. Frequently, recurrent attacks of pyelonephritis have been attributed by patient and physician to influenza because of backache and fever; sometimes they have been so slight as to be ignored and only recalled on questioning. These cases can be discovered only when pyelonephritis is suspected as a cause of obscure fever or chronic illness characterized by indefinite abdominal or lumbar distress.

Patients showing persistent or recurrent albuminuria, pyuria or cystitis should be examined for upper urinary tract infection. Urograms or retrograde pyelograms occasionally show blunting of the calices or distortion of the renal pelvis. When such changes are present they tend to confirm the diagnosis. However, more often than not, these studies show no abnormality and the diagnosis is made from repeated urine cultures and examinations of the urinary sediment.

Unfortunately, pyelonephritis can be moderately active and reveal slight or sporadic pyuria and proteinuria. Sterile urine cultures are notoriously frequent among patients who have active infection in the kidney substance. When these conditions prevail only repeated examinations and the demonstration of diminished renal function will lead to a proper diagnosis.

Appraisal of renal function is best made by the Addis test and urea clearance. The Addis test reflects tubular function in terms of ability to concentrate urine and defines the degree of proteinuria in grams per 24 hours. The Addis count detects and quantitates pyuria and hematuria not always apparent on routine examinations. Furthermore, if the leukocytes are examined with vital stains, or under the phase microscope, the degree of protoplasmic motion can be estimated. If extensive, active infection may be assumed. The urea clearance is a reliable measure of filtration rate.

In pyelonephritis, as compared with glomerulonephritis, the concentrating ability of the kidney is usually fairly well preserved. Unless the damage has been extensive the specific gravity of urine collected for the Addis test will exceed 1.018. Proteinuria is most pronounced during active infection but it is rarely extreme and ranges from 0.5 to 2 Gm. per 24 hours, while patients with glomerulonephritis and intercapillary glomerulosclerosis often excrete 3 to 10 Gm. per day. Pyuria is nearly always present when pyelonephritis is active and can reach 20 to 30 million white blood cells per 12 hours. During periods of quiescence the count may range from 1 to 5 million. Hematuria is occasionally gross during acute infection but usually it is slight or absent and never is observed constantly as in glomerulonephritis. Excessive cylindruria is an

uncommon finding save during severe attacks of inflammation. When casts are present they are granular and cellular in appearance.

The urea clearance is depressed in proportion to the concentrating power, in contrast to the proportionately greater decrease in filtration rate which characterizes glomerulonephritis and intercapillary glomerulosclerosis.

Nephrosclerosis of essential hypertension and arteriosclerosis cause renal functional changes similar to those of chronic pyelonephritis. Moreover, pyelonephritis at times induces arterial hypertension. To differentiate these cases one must depend upon history of recurrent urinary tract infection, pyelographic demonstration of ureteral or pelvic distortion, or the demonstration of bacteria in the urine. A strong family history of hypertensive disease or arteriosclerosis will encourage the diagnosis of primary vascular disease and conversely, if there is no such history, the evidence will favor infection as the cause of an obscure condition characterized by slight proteinuria, pyuria and diminished renal function.

Treatment

Once the diagnosis is made and the offending organism is known and maintained in culture, treatment with sulfadiazine or one of the proprietary preparations which furnish sulfadiazine, sulfamerazine and sulfathiazine in a single tablet, can be started. These drugs are preferred because they can be effective against both coccal and bacillary organisms and are infinitely less expensive than aureomycin, streptomycin or chloromycetin. They can be taken orally for months if necessary. Initial dosages should be sufficient to obtain concentration of 6 to 8 mg. per 100 cc. of blood. Four Gm. at the onset and 1 Gm. every 4 hours thereafter with equal parts of sodium bicarbonate are usually adequate. Fluid intake of 3000 cc. or more per day promotes satisfactory urinary drainage and discourages crystal formation. Inasmuch as many of these patients excrete the sulfonamides poorly because of renal damage, the blood concentration should be measured daily during intensive therapy.

At the same time, the sensitivity of the culture to sulfadiazine and to the antibiotics should be determined in vitro. If its growth is not inhibited by the sulfonamide, a more desirable drug can be substituted. Should the sulfonamide be effective, it may be continued until the patient is afebrile for 48 hours. Thereafter, dosages of 0.25 to 0.5 Gm. four times daily maintain urinary concentrations of 50 to 100 mg. per 100 cc. These are usually effective against recurrence and reinfection. In most cases it is wise to prolong this schedule for 6 to 8 weeks after all signs of infection are gone.

Patients who have pyelonephritis have a chronic disease, or at least are vulnerable to a recurrence with any subsequent illness, operation or pregnancy. If they are aware of the early signs of urinary tract infection and seek treatment at the first suggestion of recurrence, much distress and kidney damage can be prevented. For those who have measurable loss of renal reserve and recognized long-standing infection, an Addis examination and urine

culture at intervals of 3 to 6 months may detect recurrences that are devoid of symptoms.

Summary

Pyelonephritis is the most common of the nephropathies (5.6 per cent of 3607 routine autopsies), and is the only one that is remediable. In cases in which urinary stasis is due to a surgical lesion, diagnosis is relatively simple by cystoscopy, pyelography and urine cultures. Correction of the surgical lesion usually makes eradication of the infection comparatively easy.

In primary pyelonephritis, diagnosis depends upon adequate investigation of the patient's history, Addis examinations, urea clearance and repeated urine cultures. When the organism is identified, treatment with sulfonamides should be started, and the sensitivity of the organism to antibiotics can be determined simultaneously. If growth of the culture is not inhibited by sulfonamide, a more effective drug may be substituted.

Pyelonephritis is a chronic or recurrent disease and measures should be taken to prevent further kidney damage.

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PRIMARY CLOSURE OF THE POSTERIOR WOUND AFTER COMBINED ABDOMINOPERINEAL RESECTION FOR CARCINOMA OF THE RECTUM

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DESPITE the fact that most carcinomas of the lower sigmoid colon can now be resected safely and effectively with preservation of the rectum, the safest and most effective treatment of cancers located at or below the reflection of the peritoneum remains the combined abdominoperineal resection. This operation includes a wide resection of the rectum, the rectal stalks and part of the levator ani muscles.

Until recently we dealt with the posterior wound by packing it open, following the technic developed by Miles and Jones. Although the patients did well from the standpoint of mortality, early ambulation was hindered by the presence of the large pack. The dressing of the posterior wound required much time, caused considerable discomfort, and often drainage persisted for several months during which the patient required perineal dressings and periodic examinations to insure against the formation of an abscess.

Impressed by reports of others[1,2] who had partially closed the posterior wounds and left them drained only by a Penrose drain, we began in 1947 to close the wounds tightly by the following technic.

Technic

1. Conventional Miles type of combined abdominoperineal resection following Jones' modifications of technic, but mobilizing as much pelvic peritoneum as possible to help fill the dead space.

2. Complete hemostasis of posterior wound by electrocoagulation or ligation of bleeding points with Number 60 cotton.

3. Partial closure of stumps of levator ani muscles, fascia and fat, under tension if necessary, with 4 interrupted sutures of Number 31 stainless steel wire. This procedure reconstructs the pelvic floor, affords protection against the development of perineal hernias, and helps to obliterate the dead space.

4. Tight closure of the skin with interrupted vertical mattress sutures around a Number 12 soft rubber catheter which is inserted into the dead space and brought out at the most dependent, anterior portion of the wound.

5. Two hundred thousand units of penicillin dissolved in 20 cc. of normal saline is instilled through the catheter and the catheter plugged.

Postoperative Care

The patients are encouraged to be up and walking on the day of operation and thereafter. Four hundred thousand units of long acting penicillin is administered twice a day for 4 days. The colostomy is opened on the first postoperative day, and diet is increased as tolerated. The urethral catheter is removed on the first postoperative day, and the patient catheterized for urinary residual twice a day until the residual is below 100 cc. on two consecutive occasions.

Three times a day, the catheter in the posterior wound is opened and aspirated of any serum which has collected. A solution of penicillin in saline, 500 units per cc., is then instilled into the catheter, the amount being one half the volume of serum aspirated. Initially 100 to 150 cc. of serum is aspirated, but by the fourth day the residual dead space has so contracted that no more than 20 to 30 cc. of serum can be aspirated. The catheter is then removed and the skin edges about it are pulled together with a suture that was placed at the time of operation. The sutures are not removed until the tenth postoperative day, at which time the wound is well healed and the patient is able to walk and sit with no discomfort.

Most of the patients are able to leave the hospital on the twelfth postoperative day, competent in the care of their colostomies, eating an unrestricted diet, and with their posterior wounds firmly healed and requiring no dressings.

Results

Since this technic has been adopted, it has been possible to close the posterior wound of all except 2 of 25 consecutive cases of carcinoma of the rectum subjected to combined abdominoperineal resection. One of these patients had an extensive carcinoma of the anal canal with numerous infected fistulous tracts and carcinomatous implants necessitating too wide an excision to permit closure. The other patient, severely diabetic, was operated upon early in the series before we had full confidence in the method of closure, and the posterior wound was packed open.

Of the 23 cases in whom the posterior wound was closed 2 developed serous drainage after the catheter had been withdrawn. A small catheter was replaced, and the patients were discharged with the posterior wound well-healed except for a small sinus tract which healed promptly. A third patient developed a definite infection of the posterior wound 4 days after removal of the catheter, but this was promptly controlled by reinsertion of the catheter and instillation of a solution of penicillin in 10 per cent urethane. The patient was discharged on the twelfth postoperative day with the catheter in place and the cavity holding less than 5 cc. of clear serum. In a fourth case, a patient with hepatic metastases in which a palliative resection had been performed, the posterior wound closure disrupted and was treated in a method similar to cases in which the wound had been packed open from the onset. In a fifth case a superficial stitch abscess occurred but there was no infection of the main cavity. Eighteen of the 23 patients had firm, well-healed, wounds on

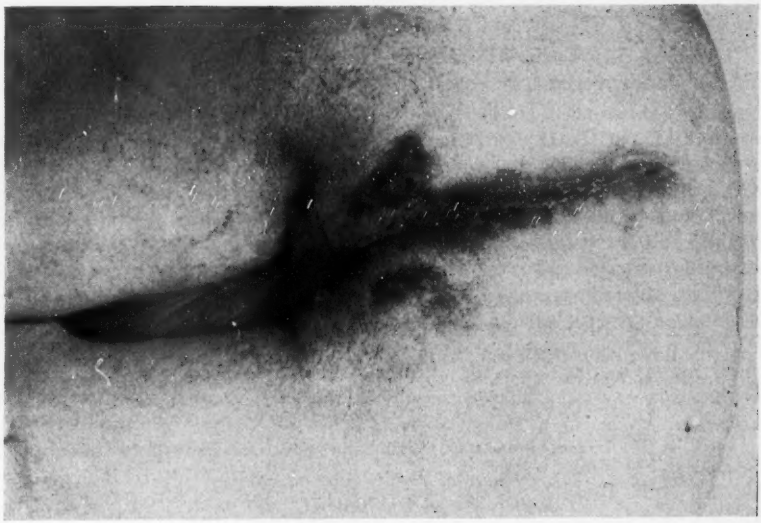

FIGURE. Posterior wound in male patient on tenth postoperative day.

the tenth postoperative day and developed no subsequent complications (figure).

No perineal hernias, weakness, or complications other than those discussed have occurred. There have been no deaths. The average postoperative hospital stay in uncomplicated cases has been twelve days.

Advantages:

1. Nursing care is facilitated by early ambulation and reduced necessity for posterior wound dressings.
2. A closed wound free of infection is comfortable and avoids danger of secondary infection, collection of loculi of pus in upper portion of wound, and irritation of pelvic peritoneum by a pack.
3. Convalescence is shortened and care after discharge from the hospital is greatly simplified.
4. Physiologic bowel and bladder function are re-established earlier, as a result of ambulation.
5. Anticoagulants are rarely necessary because patients are ambulatory from the time of operation.
6. Economic rehabilitation is not delayed by a gaping posterior wound.

Disadvantages:

Careful hemostasis and closure of the posterior wound increases the operative time by about 30 minutes. The average operating time from initial incision to final sutures is 1 hour and 45 minutes.

Summary

1. A technic for primary complete closure of the posterior wound of combined abdominoperineal resection of the rectum is presented.

2. In a series of 25 consecutive cases, it was possible to close the posterior wound in 23. (a) In 18 cases the posterior wounds were completely healed in 10 days. (b) In 2 cases, the posterior wound was well healed except for a small sinus which healed promptly. (c) In 1 case the posterior wound disrupted and was allowed to heal by granulation. (d) In 1 case the posterior wound became infected and the catheter was reinserted. (e) In 1 a superficial stitch abscess occurred.

3. There have been no deaths in this series.

4. The patients have been ambulatory from the day of operation, and the majority have been discharged on or before the twelfth postoperative day.

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DRUGS ON THE MARKET*

TORALD H. SOLLMANN, M.D.**

THE first essential in appraising a drug, personally or by proxy, is to judge the possibility of bias, which takes so many forms. The crudest form, financial interest, is almost necessarily present in the case of statements of drug firms. It may be crude indeed, in which case, it generally may be spotted by all but intellectual infants. But it can be assumed that even the best-intentioned firms are not blind to the interests of their stockholders, and are so hopeful of making a "strike" that they are likely to err on the optimistic side, once they are committed to marketing a drug. This does not necessarily disqualify their evidence, but it instinctively should enjoin extra caution in appraising their estimate, especially that of the salesmen who are quite apt to go somewhat further than the firm itself.

"Controls" are the one method by which an honest investigator can eliminate personal bias, conscious, unconscious or accidental. But when are controls "adequate" in kind and in degree? The answer is, "that depends." It varies for each case. As to kind, they must be such that they cannot be modified at the whim of the investigator. That means usually a "blind" test, such as comparison with a placebo or an established drug with the conditions set down in advance, so that the investigator is left no discretion, once the series is started; for instance, alternate admissions receive the drug to be tested, the other the placebo. Of course, patients must be comparable, but as no 2 patients are alike, this may not be a simple situation. It may be necessary to "stratify" them into grades, perhaps by the degree or duration of the disease, alternating the patients in a given stratum.

The question of adequacy of the controls depends on the natural variability of the "blind" placebo series, and may require the aid of a statistician. The statistician can work only with the data submitted to him, and may not be able to judge whether these data are good or bad. The responsibility, therefore, depends upon the competence and good faith of the investigator. Statistical analysis can go no higher than its factual source—and sometimes not that far.

Drug manufacturers are under constant drive for multiplication of remedies as such, even if this is mere duplication. They naturally wish to share the harvest while the sun is shining; they do not wish to seem behindhand; they feel that they must match all promising drugs, lest they be thought unprogressive. This drive has a good feature; it motivates research, and it brings out improvements that may be worth-while. It has its bad aspects, in that it

* *This is an abbreviation of a talk given before the Staff and Fellows at the Cleveland Clinic on October 10, 1949.*

***Chairman, Council on Pharmacy and Chemistry, American Medical Association.*

wastes effort, not only on the part of the manufacturers, but of the physicians who are urged to try new and unproved drugs, worthless though they may be. The good and the bad in multiplication are delicately balanced, but the interests of the manufacturers incline to stress multiplicity, while those of the physician and the public favor simplification—the elimination of superfluous duplications and equivalents. Barbiturates are an example of the benefits, for while manufacturing enterprise has resulted in many superfluous duplications, it has also brought out distinctive differences that are practically useful. The antihistamine drugs and the sex hormones, on the other hand, are instances where multiplication has resulted chiefly in confusion and wasted effort. The situation can be greatly simplified by adhering to certain criteria to insure the essential objectives that make a new drug worth-while, namely, its advantage over the current drugs, rather than the superficial differences which are a trap for the unwary.

These criteria have been summarized in a Report of the Council on Pharmacy and Chemistry:

(1) **Potency:** In a new drug asserted to be more potent, the difference should be material. A gain of potency, even of 100 per cent, signifies little if the same ends are secured simply by increasing the dosage of the weaker drug, unless it also means a relative decrease in undesirable side actions, material reduction in cost, or some similar benefit.

(2) **Lesser toxicity**: This has a practical meaning only if the margin of safety—the ratio of therapeutic dose to the dangerous dose—is materially greater. No advantage is gained, for instance, if the toxic dose is ten times that of the old drug and the therapeutic dose of the new drug is also ten times higher. Likewise, a gain of 10 or even 50 per cent in the fatal dose is of no material advantage if the toxic dose of the old drug is so far from the therapeutic dose that the toxic level would never be attained in practice. Nor is anything gained if the additional margin of safety of the new drug is only 10 or 20 per cent greater than that of the old drug, unless the therapeutic and toxic doses are approximate.

(3) **Freedom from side actions** is generally only relative, and has no practical significance unless sufficient in kind or in degree to be pertinent.

(4) **Cost** may well be relevant, especially with the more expensive drugs. Unfortunately, the newer drug, more often than not, has little effect on material economies.

Another confusing problem of multiplication is the duplication of names for identical products, imposed by the imperative financial necessities of the drug firms. A firm that develops a really new drug generally makes a large investment in research and promotion expenses. If it is to fulfill its obligations to its stockholders, it must regain the expenditure, plus a substantial profit, as well as the outlay on experimentation with substances that prove ineffective after they are marketed or never reach the market. To meet this inescapable fact, the firm tries to protect itself against the competition of those who would reap the harvest without having financed the experiments. This protection

is furnished by patents and especially by trademarks, for patents expire in 17 years after which anyone is permitted to produce and market the product, but trademarks endure. A trademark signifies a distinctive name or device that identifies the product of that particular firm. To further establish this identity there must also be a common name which may be employed by manufacturers after the patent expires, a name in actual use some time before the expiration. The originating firm introduces this common or generic name, preferably at the time its trademarked brand name is introduced, in addition to the chemical name, which usually is complicated. We have at least three names initially. The chemical name is supplied by the chemists. The firm, understandably, stresses the brand name, which is short and easily read, pronounced, written and remembered. This involves some ingenuity, for there are already so many names on the trademark list that it is difficult to find one that does not conflict. Moreover, the Council on Pharmacy and Chemistry will not accept a trademark that suggests therapeutic use, because it often is or becomes misleading. The Council urges that the generic names suggest the chemical structure, although it is not always feasible to do this and still provide a name practical for prescriptions.

The name must not misrepresent the chemical structure. The manufacturer naturally tries to accustom the physician to the use of its brand name, but too much emphasis must not be placed upon this, lest the courts assume it to be the common name and cancel the trademark, as in the case of Cellophane. They are, therefore, obliged to carry water on both shoulders—a heavy bucket for their brand name on the right, and a little tin cup for the generic name on the left shoulder. The physician is strongly impelled to use the brand name, which is so prominently displayed; he would do better to use the generic name in his thinking and in his writing. When the patent expires, and competing and generally cheaper brands become available, these cannot be sold under the original trademark name. The United States Pharmacopeia and National Formulary do not recognize brand names when the product becomes official, but use the generic name, now usually the one originally adopted by the Council on Pharmacy and Chemistry. The United States Pharmacopeia does not mention adrenalin or novocain, for example, but epinephrine and procaine. When a physician states that he injected adrenalin or novocain, he infers that he used these particular brands, which suggests, absurdly, that our suprarenal glands manufacture epinephrine by courtesy of Parke Davis and Company.

Let us assume that the patent on a good drug expires, and other manufacturers are free to make it, but not under the original brand name. They could do so under the unrestricted generic name, but infrequently do. While this was the original objective of the Council on Pharmacy and Chemistry, manufacturers were uncooperative, and perversely sold the product under new brand names of their own because it was good business financially. A manufacturer will not sell much nowadays, unless he advertises; if he advertises only under the generic name, his competitors will also reap the profits. Therefore he aims to protect himself by trademarking a brand name of his own.

Lest the Council lose all control over his product, it seemed the lesser evil to permit additional brand names—until a substance became official in the United States Pharmacopeia or National Formulary. That sets a time limit, at least, on multiplication, and the physician can always avoid confusion by becoming accustomed to the use of the generic name, which covers all brands.

There is the dilemma: on the one hand, a personal investigation of the original literature, which requires experience, special skill, critical judgment and much time; on the other hand, the shortcut offered by the manufacturers, easy, smooth, and beset with bias. The perplexed physician needs help in the appraisal of new drugs, but it must be honest, unbiased, well-informed, and critical. Fortunately, this help is easily available.

There is, in the first place, the United States Pharmacopeia. There was a time, within my experience, when it was the confessed policy of the United States Pharmacopeia to accept anything extensively prescribed, making extent of use the sole criterion of merit. This policy gave no consideration to whether the use was based on adequate criteria or merely on vogue, superficial impressions that had never been critically tested. Moreover, it did not contain the newer drugs, only those which had aged for at least 10 years. Thus the United States Pharmacopeia was of no great help in the selection of drugs. All this has now been changed; the selection is made by the medical members of the Revision Committee, on the basis of informed advice when there is any question. Therefore a drug which is now in the United States Pharmacopeia is fairly certain to be worth-while. The publication is to be revised every 5 years instead of 10, so that it will include all but the most recent important drugs. Other signs of progress include the emphasis on English instead of obsolete Latin titles, and the preference of the metric over the common system in weights and measures. These changes are most encouraging to those of us who solicited them through some decades. The next United States Pharmacopeia convention will be held in May, 1950, and it is hoped that medical organizations will show their appreciation and interest by sending delegates. The National Formulary has also been greatly improved, but is less critical. One limitation of both books from the standpoint of the physician is that they give no information whatever about actions, or whether the drugs are valuable for a given purpose. Aid with the newer drugs is the special field of the Council on Pharmacy and Chemistry, which has operated continuously and successfully for more than 43 years. It consists of 17 members, appointed by the Trustees of the American Medical Association, from nominations presented by the Council. Members are selected for their general reputation of high ideals and practical wisdom, combined with outstanding knowledge and experience in their special field. They serve for long terms, generally as long as they are able and willing to give the time that this work requires. Technical questions outside of the experience of the regular members are referred to the special consultants. The Council has a full-salaried executive secretary, Dr. Austin Smith, and under him several carefully chosen full-time professional and clerical staff assistants. The well-staffed and equipped Chemical Laboratory of the American Medical Association is in close relation with

the Council on Foods and Nutrition, Physical Therapy and other departments. When a new drug appears on the market, the headquarters staff gathers all pertinent information from the manufacturers and from other sources. This is presented to the referee, who prepares a comprehensive critical report as to the properties of the drug, its actions and uses, and whether the claims made for it are fully justified by the evidence. The Council then votes whether it should be accepted, rejected, or should await further investigation. If it is accepted, a careful description is published in the Council columns of the Journal of the American Medical Association, and reprinted in the annual New and Nonofficial Remedies. If further evidence is necessary, the manufacturers are given opportunity to supply it. If the drug seems of sufficient importance, an interim status report is published in the Journal.

Acceptance may be taken as assurance of the drug's value and its purpose in the light of existing knowledge. It does not indicate that it is the best drug for any purpose, for that varies with conditions, but it does give reliable and unbiased information from which the physician can determine upon consulting the annual New and Nonofficial Remedies, how it best suits his particular need. If the drug is recent he may refer to the current issues of the Journal of the American Medical Association. If he does not find it there, he may write to the Council at the American Medical Association in Chicago, and he will receive the available information. Meanwhile, he may save himself time, trouble and disappointment by asking the salesman whether his drug has been accepted by the Council. If it has not been accepted, it usually means that adequate evidence is not yet obtainable. The Council on Pharmacy and Chemistry demands that the manufacturers supply such information with good evidence for their claims. If this requires extensive cooperative clinical investigation, and if it appears of sufficient importance, the Council may arrange research through its Therapeutic Trials Committee. The most important project engaged upon at the present time is the evaluation of the field of sex hormones in the treatment of malignant tumors.

To summarize, you may protect yourselves from being victimized by "Drugs on the Market" in the bad sense, and secure the full benefit of "Drugs on the Market" in the best sense, by adhering to the following principles:

1. Restrict your prescribing to the smallest number of drugs sufficient for your needs.

2. Do not "try" a new drug unless you have a good reason.

3. Scrutinize carefully before you add needlessly to the drugs with which you are already familiar.

4. Insist that a new drug has been thoroughly studied before you try it.

Do not make up your mind, and especially do not give scope to your tongue or pen, unless and until your conclusions can stand up before critical judges. Until then, cultivate the priceless quality of personal reticence. The publication of a few false judgments that could have been avoided may blast a professional reputation, sometimes beyond repair. There is more risk of harm in talking too much than too little.

INTRACRANIAL MENINGIOMA FOLLOWING TRAUMA

Report of a Case

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WITH any subject as controversial as that of traumatic and post-traumatic tumors, critical analysis of case histories and physical findings is essential. Strict criteria must be established, against which the data on each patient may be tested, and these are detailed by Ewing[1] as the following:

(1) the adequacy and authenticity of the trauma must be established;
(2) the previous integrity of the injured part must be confirmed;
(3) the tumor must originate from the exact site of the injury;
(4) there must be a reasonable lapse of time between the injury and the onset of the tumor symptoms, and
(5) a positive diagnosis of the nature of the tumor must be made.

If such a test were applied to all recorded cases of tumor following trauma, much confusion could be avoided.

Case Report

A 59-year-old man was referred to the Cleveland Clinic on August 19, 1949, with the complaint of repeated convulsive seizures. The relevant history concerned an automobile accident 21 years previously, in which he had sustained cerebral concussion and a depressed fracture in the left frontoparietal region. The calvarial depression had never been elevated.

Following recovery from the immediate effects of the accident, he had been completely free from symptoms until approximately 1 year prior to the present examination. At that time while in bed and apparently asleep, his wife had noticed that he was making clutching movements with both hands. She spoke to him, got no response, and was unable to arouse him. The attack developed into a generalized tonic seizure followed by flaccidity and unconsciousness for approximately 15 minutes. When he awoke he was apparently perfectly normal, with no headache. There had been no generalized clonic phase, no lateralizing sign, no incontinence of bladder or bowel, and no aura.

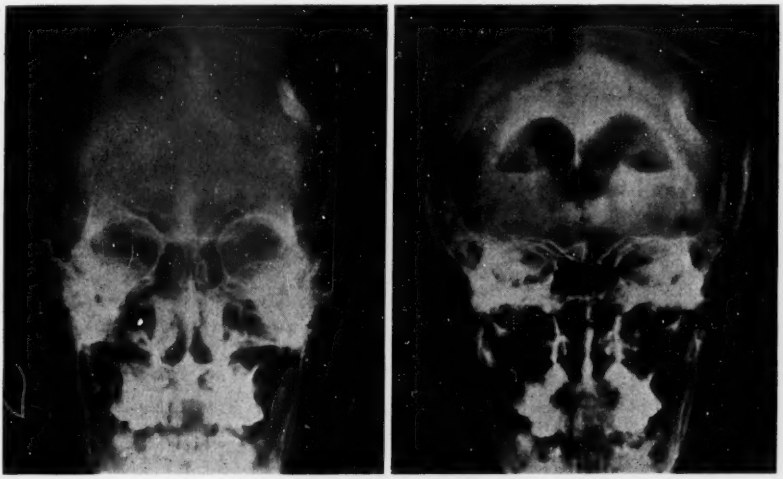
Similar attacks had occurred about ten times during the year following the original episode. The later spells had occurred during waking hours, accompanied by a short aura of lightheadedness and an indescribable odor, and commencing with a tonic turning of the face to the right side and jerking movements of the right arm. The duration of each episode was about 15 minutes, and there was no subsequent paralysis or headache.

The family history was clinically unimportant and the patient's previous medical history showed no relevant factors except the remote possibility of beryllium toxicity, as he had been exposed to this substance while working in a foundry for several years.

General examination disclosed a well-built man with a normal mental status. He had a circular depression in the left frontoparietal region about ⅜ inch deep and 2 inches in diameter.

Neurologic examination on August 19, 1949, revealed no abnormal signs and no evidence of disease of the central nervous system. There was no papilledema. Roentgen films of the skull showed evidence of an old depressed fracture in the left frontoparietal area (fig. 1a).

An air encephalogram on September 1, 1949 (fig. 1b), showed dilatation of both lateral ventricles and the third ventricle with a slight displacement of the whole ventricular system to the right. The cerebrospinal fluid was not under increased pressure, and contained 41 mg. of protein and 1 cell per cu. mm.



(a) (b)

FIG. 1. (a) Plain skull film showing evidence of old depressed fracture in left frontoparietal region. (b) Air encephalogram showing dilatation of lateral ventricles and third ventricle with slight displacement of midline structures to the right.

Electro-encephalogram showed a borderline record with no evidence of a focal, cortical lesion.

It was our diagnostic impression that the depressed fracture was the cause of the patient's Jacksonian convulsive seizures.

On September 2, 1949, an operation was performed for the purpose of elevating the depressed calvarial fragment. The description of the operation reads as follows:

"A large scalp flap was turned down around the old depressed fracture in the left frontoparietal area. The depressed portion of the skull was about 2 inches in diameter and was situated directly over the motor arm area on the left side. The depression was about ⅜ inch deep and the bone fragments had healed firmly during the 20 odd years since the injury. A drill hole was made through the center of the depressed area and the depressed bone was gradually removed by means of a rongeur until there was a bony opening about 3 by 2.5 inches in size. The underlying dura was quite adherent to the

inner depressed table of the skull but no fragments of bone had broken through the dura. The bone was thick and avascular and extremely hard at the site of the depressed fracture. The underlying dura was somewhat vascular and tense. The operator decided to open the dura in order to examine the cortex and to determine the presence or absence of adhesions between the dura and the cortex. The thickened dura was opened with a curved incision and a flat retractor was placed beneath it in an upward direction toward the sagittal sinus. At a point just beneath the site of the old depressed fracture, the retractor met resistance. It was the operator's impression that the retractor had encountered some adhesions between the cortex and the dura. The dura was then opened more widely in an upward direction, and to the surprise of the surgeon, a tumor was encountered at the exact location of the previous depressed fracture; an encapsulated meningioma slightly larger than a robin's egg attached to the dura was lying in a pocket of the cortex in the motor arm area. The dura was cut through all the way around the base of the attachment of the tumor and the tumor was gradually separated from the cortex by cotton dissection. The neoplasm was easily removed in one piece with its overlying dural attachment. There was no excessive bleeding. The tumor had the gross appearance of a meningioma (fig. 2). The dura was partially closed with interrupted nylon sutures.

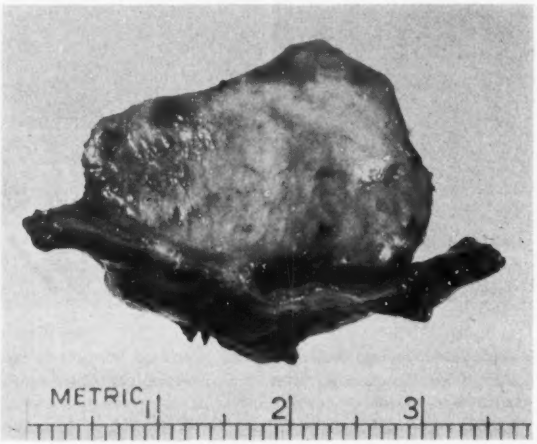


Fig. 2. Meningioma after removal, complete with its dural attachment.

A tantalum plate about 3 by 4 inches in size was fashioned and screwed down to the skull with four tantalum screws, covering the bony defect. The scalp flap was then replaced over the tantalum plate and united in layers with interrupted black nylon sutures. Microscopic examination of the tumor revealed a meningioma of meningothelial type."

Discussion

For many years the relationship between trauma, irritation and neoplastic growth has been debated, and in the case of the intracranial tumors, no less than with neoplasms of other organs, authorities have differed widely in their views.

Stewart[2] disapproved of attempts to correlate the incidence of a single injury with subsequent cancer. Ewing[1] believed that coincidence is of greater importance than is generally recognized.

It must be remembered that a tumor may be the indirect cause, rather than the effect, of trauma. This is especially true with intracranial new growths, in which disorders of equilibrium, visual defects and convulsions may lead to head injuries.

Thus, even though injury may occur over the site of a neoplasm and may be followed by the onset of signs and symptoms referable to the growth itself, the traumatic incident should be regarded as an aggravating rather than a causative factor. The aggravation in these cases is usually believed to be the result of edema or hemorrhage in the tumor area. In fact, a small proportion of previously undiscovered intracranial neoplasms is disclosed in this manner.

Many authorities now appear to believe to some extent in the possibility of tumor formation following chronic irritation.

Keen and Ellis[3] in 1918 described a case in which a depressed fracture of the skull involving both tables was followed about 20 years later by manifestations of irritation and compression of the brain. These symptoms were shown to be due to neoplasm. The tumor lay directly beneath the area of the depressed fracture and was diagnosed at that time as a fibroma. Complete removal was effected, and the patient survived the operation by 30 years. Keen's opinion was that the constant motion of the brain and dura, due to arterial and respiratory pulsations, caused friction against a spicule of bone fractured from the inner table, and gave rise to the tumor.

Cushing and Eisenhardt[4] supported the view that the importance of trauma could not be overlooked. They believed the relationship between a blow on the head and the location of an ensuing meningioma to be so precise as to make the conclusion inescapable that an etiologic factor was involved. In support of this belief they quoted several case histories, and noted that almost one-third of their patients with meningiomas at that time had an associated history of trauma. Among these cases was the interesting history of General Leonard Wood in whom the onset of Jacksonian attacks occurred 4 years after a blow on the vertex, and from whom a neoplasm was removed. Cushing and Eisenhardt also call attention to another interesting case in which an apparently normal dura was exposed at operation for removal of thickened bone at the site of an old fracture. Three years later a meningioma was found at exactly the same site. In this case the onset of symptoms occurred 10 years after the original injury. Other cases of parasagittal tumors quoted by Cushing and Eisenhardt show a somewhat convincing relationship between injury and symptomatic onset.

As a result of observations on these and other cases, Cushing and Eisenhardt suggested the following factors which might play a part in the pathogenesis of such neoplasms. "(1) A local contusion of the bone; (2) a bruised meninx most likely to occur along a suture line; (3) a local outpouring of meningocytes to take up the extravasation, and (4) a pathologic continuance of their active cell division."

These factors were believed to have explained the relative frequency of meningioma at the bregma and the pterion where four suture lines meet and where there are four adherent sections of dura. However, the fact that meningiomas never result from the operation of craniotomy, in which all four conditions are probably fulfilled, would appear to militate against this theory of pathogenesis.

Confusion may be caused in some of these patients by the recognized tendency of certain types of menigioma to form bone. It may be difficult to state whether a bony fragment found to be embedded in the tumor is the cause, or one of the pathologic effects of such neoplastic growth. Undoubtedly many fractures involve the inner table of the skull, with consequent irritation of the meninges by pointed spicules or the sharp bony edges of the fracture. However, the incidence of meningioma following such injuries is low.

Summary

In the case reported a depressed fracture of the cranial vault was followed some 21 years later by manifestations of cortical irritation at the site of the old fracture. The findings at craniotomy and the other available facts suggest that the tumor originated as a direct result of the depressed fracture. It must be emphasized however that the cause of such neoplasms still remains obscure.

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MYCOSIS FUNGOIDES

An Analysis of Thirteen Cases

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THIRTEEN patients with mycosis fungoides have been seen at the Cleveland Clinic. Nine were men and 4 women. The youngest patient to develop the disease in this series was a 22-year-old woman and the oldest a woman aged 71.

Twelve of the patients were white and 1 was colored. Occupation was not significant. The duration of the disease before being seen at the Clinic varied from 1 month to 10 years.

One patient developed dermatitis venenata which was followed by a generalized exfoliative dermatitis on which lesions of mycosis fungoides developed 4 years later. Another patient had "psoriasis" for 30 years and then developed mycosis fungoides. One patient had mycosis fungoides of the d'emblee type. Nine complained of pruritus and in 3 cases this was severe. Sensation of burning was present in 1 case. Two patients were asymptomatic. Enlargement of the superficial lymph nodes was observed in 6 patients.

On admission to the Clinic 2 patients had exfoliative dermatitis; the others presented nodules, erythematous scaly plaques, ulcers, papules, and macules. Concomitant diseases were syphilis, psoriasis and carcinoma of the esophagus.

Diagnosis is often difficult. The clinical diagnosis of mycosis fungoides or lymphoblastoma was entertained in 11 cases on entrance to the Clinic. In 1 case syphilis was first considered; in the patient with the d'emblee type of lesion, three possibilities were first considered in differential diagnosis: (1) neoplasm, (2) factitia dermatitis, and (3) melanoma.

In 10 cases biopsy showed histologic pictures consistent with mycosis fungoides. Three were diagnosed as lymphoblastoma histologically but as mycosis fungoides clinically.

Complete blood studies were done on all patients. Initially all were within normal limits. Three of the patients in the series had sternal marrow examinations. All were reported as nonspecific chronic inflammation. In 2 cases lymph nodes were removed and examined but were reported as nonspecific.

All of the patients received roentgen therapy at some time during their illness. This appeared to be the one method that could be depended upon to bring a temporary improvement in most cases. There was, however, great variation in individual response. Two patients became resistant to roentgen therapy after a while. One patient had approximately a total of 11,000 r of

superficial roentgen therapy and three courses of nitrogen mustard but continued to develop lesions when treatment was stopped.

Sodium arsenate, potassium bismuth tartrate, testosterone, manganese, urethane, paraminobenzoic acid, stibanose, nitrogen mustard and transfusions were used. Two patients received three courses and 1 patient received two courses of nitrogen mustard with temporary clinical and symptomatic relief. As in the other cases reported in the literature, those patients who were given nitrogen mustard developed leukopenia and a decrease in hemoglobin and red blood cells. It was also noted that the effects from subsequent courses of nitrogen mustard were not as great as the effect from the initial course. One patient received little relief from a second course of nitrogen mustard and was given roentgen therapy for a while after which a course of nitrogen mustard was repeated. The patient responded rapidly to the therapy temporarily and then relapsed. Remissions were never complete clinically with the drug and did not last longer than 2 months. Stibanose was not as spectacular in its results as nitrogen mustard. Two out of 3 patients noted a little improvement subjectively.

Of the 13 patients, 5 have died, 6 are living and 2 have disappeared from observation. The causes of death were carcinoma of the esophagus, pneumonia, and 1 was reported to have died of leukemia. Cause of death in the other 2 is unknown. One patient has had the disease for 14 years and is still living.

Discussion

Mycosis fungoides is a chronic disease of unknown etiology, primarily of the skin, occasionally with later involvement of the internal organs; characterized by remissions, exacerbations and various clinical stages. It occurs in the latter decades of adult life, predominantly in white men.

The name is a misnomer as the disease is not of mycotic origin.

Mycosis fungoides has been included as a member of the lymphoblastoma group, which consists of Hodgkin's disease, leukemias and lymphosarcoma. Some authors have felt that these are clinical pictures of the same disease process.

Signs and symptoms vary with the stage of the disease. Severe pruritus, pricking and burning may be present long before lesions appear in the skin. Systemic symptoms as fever, anorexia, and weakness, usually do not appear until later.[1]

The disease may begin as an exfoliative dermatitis, universal erythroderma, erythematous eczematoid eruption, poikiloderma,[2,3] and later develop infiltration of the skin with the formation of tumors and ulcers. The onset can be of the d'emblee type, in which tumors develop on the normal skin without the eczematoid phase. Any part of the cutaneous surface may be involved and Oliver[4] mentions some cases in which there were metastases to the lungs, pleura, mediastinum, tracheal mucosa, epicardium, soft palate, lymph glands, and skeletal musculature.

Death may occur from 6 months to 40 or more years after onset of the disease. According to Montgomery,[1] "The average duration of life was about 5 years and longer with treatment, which is much greater than in the other types of lymphoblastoma." Spontaneous involution of tumors has occurred without treatment, and then the tumors have reappeared years or months later.

The histopathologic changes vary in the different stages of mycosis fungoides. In the eczematoid stage, there is acanthosis and micro-abscesses containing lymphocytic cells. The cutis contains a polymorphic infiltrate consisting of eosinophils, endothelial cells, plasma cells, polymorphonuclear leukocytes, lymphocytes, pseudogiant cells, histiocytes, reticulo-endothelial cells, connective tissue cells with karyorrhexis and pyknosis of nuclei. The tumorous stage resembles a reticulum cell sarcoma as the cells usually appear more uniform and monomorphic. There is definite increase of reticulum fibers in both stages and there is a proliferation of the endothelial cells lining the blood vessels in the cutis, which has been considered as proof that mycosis fungoides is a disease of the reticulo-endothelial system. It is also transformed to other lymphoblastomas, especially lymphosarcoma according to Montgomery.[1]

Numerous drugs and forms of therapy have been used but the results have all been temporary.

Summary

Of 13 cases of mycosis fungoides diagnosed at the Cleveland Clinic 1 is still living who has had the disease for 14 years. There is no permanent satisfactory treatment for mycosis fungoides at present. Roentgen irradiation seems to be the best temporary method of treatment. Nitrogen mustard in our experience was not as beneficial over a period of time as superficial roentgen therapy, and its toxic effects limit its value as a therapeutic measure in this disease.

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ARTERIOGRAPHY IN CEREBRAL ARTERIOVENOUS MALFORMATION

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THE term cerebral arteriovenous aneurysm or malformation is used to designate that type of cerebral vascular lesion in which the arterial and venous circulations are connected by a nest or cluster of racemose vessels.

Such lesions have been considered relatively uncommon. Cushing and Bailey[1] in their analysis of 2023 proven brain tumors found fewer than 1 per cent, while Dandy[2] quoted a similar figure. Ray,[3] in 1941, reported 6 cases of his own and found approximately 75 in the literature. Five cases were reported by Hodes et al[4] in 1947. However, in a series of 150 arteriograms made in a period of less than 2 years we have demonstrated 8 arteriovenous malformations. It therefore appears that this is a more common entity than was believed originally.

These malformations most often involve the middle cerebral artery and are considered congenital in origin. The arteries supplying the lesions are dilated and the associated veins are large, tortuous and pulsating. Calcium deposits in and adjacent to the vessels of the malformation are common; numerous thrombi may be present. It is these degenerative changes which predispose to subarachnoid hemorrhage and cortical damage.

The patient often presents a history of epileptic seizures, migraine type headaches, and permanent or transient paralysis of varying degree. The neurologic pattern is usually bizarre, and accompanied by such changes as cranial nerve paralysis, hemiparesis, vague sensory alterations, and visual field defects. On auscultation of the calvarium a bruit may be heard. The patient frequently is not aware of this. The eye grounds may reveal dilated tortuous vessels and papilledema which is considered the result of increased venous pressure rather than increased intracranial pressure. Spinal fluid dynamics are almost always normal and fluid examination is normal except in cases of recent subarachnoid hemorrhage. This may be the first sign of the presence of a vascular malformation. Electroencephalography is normal unless there has been some secondary cortical damage.[5]

The plain skull films show varying changes depending upon the size and location of the lesion.[4,6] Frequently the diploe are enlarged. The foramen spinosum, foramen transversarium, and the groove of the middle meningeal artery may be enlarged. The presence of dilated vessels against the calvarium results in signs of local pressure atrophy. Because of the increased vascularity an overgrowth of the bones of the calvarium may result. Calcification is sometimes seen in the vessels of the malformation and in the adjacent nervous

tissue. Only rarely signs of increased intracranial pressure are demonstrated. These are observed when the malformation involves the great vein of Galen which enlarges and produces pressure against the aqueduct of Sylvius resulting in an internal hydrocephalus.[7]

The encephalogram frequently fails to demonstrate any sign of the presence of the lesion.[8] Occasionally changes indicative of a space-taking lesion may

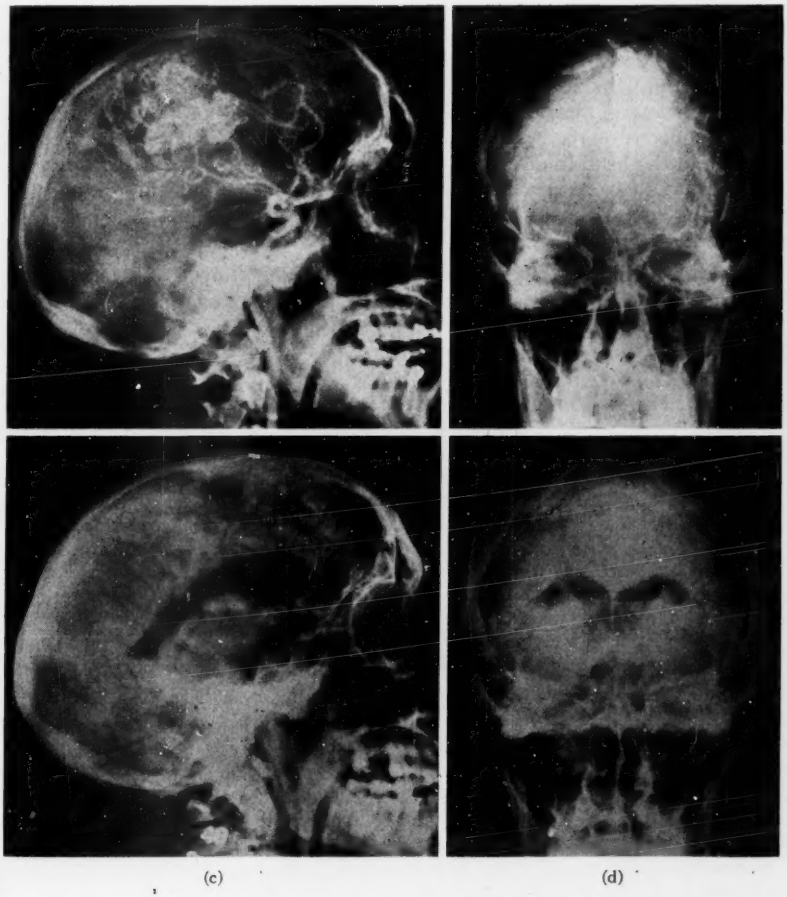

FIG. 1. (a and b) Dilated anterior cerebral artery leading to large cluster of well-developed, irregular vessels in left frontoparietal region. Associated veins dilated and tortuous. (c and d) Lateral ventricles slightly larger than usual and cortical sulci slightly exaggerated.

be present but a specific diagnosis is not usually possible. Ventriculography is considered dangerous because of the possibility of puncture of one of the involved vessels.

Cerebral arteriography offers a means of positive preoperative diagnosis of arteriovenous malformation and enables one to evaluate the lesion accurately and to decide upon the proper course of therapy. The nest of dilated dye filled vessels is easily recognized. Usually both arterial and venous components are visualized in the arterial phase of the arteriogram due to the accelerated circulation time.

The technic of arteriography is neither difficult nor dangerous. It is best performed under general anesthesia. Sodium pentothal is used routinely at the Cleveland Clinic. We prefer the use of 35 per cent diodrast as a contrast medium because of the somewhat questionable danger of thorotrast.[9] The closed or percutaneous method of injection is employed routinely. With the patient supine and the head immobilized with adhesive tape on a radiolucent rest an 18 gauge needle is inserted into the carotid artery. Ten cc. of diodrast is injected rapidly. A lateral film is made, diodrast is injected again and a posterior-anterior film is made.

Several methods of therapy are used in the treatment of arteriovenous malformation.[2] Among these are carotid artery ligation, decompression, surgical removal, and roentgen therapy.

Case Report

A 33-year-old white man was first seen at the Cleveland Clinic on October 18, 1948, complaining of weakness of his right hand and foot of 2 weeks' duration. He had first experienced difficulty 12 years previously when he awakened suddenly and noticed numbness of the right hand, and tingling of the right shoulder, right leg, and right side of the trunk. He lost consciousness for about 15 minutes and was later informed that convulsions had involved the right side during this period. At the same time the tongue was injured. Subsequent treatment consisted of anticonvulsant medication. For the next 10 years he experienced attacks of a similar nature annually. Two years prior to admission medication was interrupted for several days and he underwent a severe attack which lasted between 20 and 40 minutes; thereafter the attacks were increasingly frequent. Two weeks before admission weakness of the right extremities was first noted.

Past medical history was not significant, nor was family history.

Neurologic examination revealed an absence of deep and superficial reflexes over the left side of the body and diminished or absent reflexes over the right side. There were no pathologic reflexes. There was a lack of co-ordination on the right in response to finger to nose and heel to knee tests. The left side of the face and right side of the body showed slight impairment of sensation to pain and touch; the left temporal region was slightly tender. There was a paresis of right upper and lower extremities. The right hand and foot showed pallor and there was some unsteadiness and deviation of gait to the right.

A spinal puncture was performed. Dynamics and fluid examinations proved to be normal. Urinalysis and blood studies revealed no abnormalities. Visual field examination was slightly suggestive of bitemporal defect. An audiogram was normal.

Because of the long history of Jacksonian seizures in this case, a vascular anomaly was suspected and arteriography decided upon.

A left carotid arteriogram (figs. 1a and b) showed a dilated anterior cerebral artery leading to a large cluster of well-developed, irregular vessels in the frontoparietal region sharply demarcated at the midline. Associated veins were diluted and tortuous.

An encephalogram (figs. 1c and d) revealed lateral ventricles which appeared somewhat larger than usual with cortical sulci slightly exaggerated.

The diagnosis was arteriovenous malformation and roentgen therapy was considered the treatment of choice. Sufficient time, however, has not elapsed for evaluation.

Summary

The case described demonstrates the classic findings of intracerebral arteriovenous malformation. A large malformation is demonstrated on the arteriogram. However the lack of specific change on the encephalogram illustrates the inadequacy of air studies in lesions of this type.

We believe that cerebral arteriography is indicated in all cases which present a perplexing neurologic problem and particularly in those with a history of epilepsy or spontaneous subarachnoid hemorrhage.

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LYMPHEDEMA

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ALTHOUGH lymphedema is not a common cause of swelling of the extremities neither is it rare, and occasionally the family physician is consulted by an anxious adolescent girl who complains of progressive swelling of the legs. Too often the physician knows little or nothing about the condition and is inclined merely to sympathize with the patient whose symptoms indicate eventual "piano legs" or elephantiasis. It is true that once the end stage of intractable, fibrous edema is reached, treatment is generally unsatisfactory; however, initiated early in the disease it is usually successful, and will in most cases, keep the edema under control and avoid the adverse psychologic patterns often encountered in a woman with unsightly legs.

General unawareness of the entity of lymphedema stems from the fact that little has been written on the subject and consequently it is passed over lightly in medical schools and textbooks. In recent years the excellent works of Drinker and Field[1] on the anatomy and physiology of the lymphatic system, and Allen[2] on the classification, etiology and differential diagnosis based on 300 cases at the Mayo Clinic, have done much to clarify and simplify the previous confusion concerning lymphedema.

Definition. Lymphedema is an abnormal accumulation of lymph in the soft tissues. It is characterized by swelling, usually of the extremities, in the early stages, and by so-called elephantiasis, the result of continued edema and fibrosis, in the late stages. It is generally conceded that the term elephantiasis should not be used synonymously with lymphedema since it is merely a descriptive term which aptly describes the end result of a variety of conditions.

Mechanism. The accumulation of lymph in the tissues is due to obstruction of lymph flow caused by noninflammatory or inflammatory processes. Homans, Drinker, and Field[3] have shown that, as the lymph collects, there is a steady increase in its protein content (to 3 or 4 per cent in 5 patients). As the concentration begins to approach that of serum there is an active proliferation of fibroblasts and eventually increasing fibrosis of the deep layers of the skin and subcutaneous tissues. The fibrosis causes further stasis and the whole process becomes a vicious cycle. The stagnant lymph is subject to recurrent attacks of acute inflammation. This results in thrombosis of lymph vessels and further stasis. The terminal result is a proliferative, intractable swelling (elephantiasis) of the extremity.

Classification. The largest series of cases of lymphedema studied was reported by Allen[2] in 1934. He made a detailed study of 300 cases seen at the Mayo Clinic over a 10 year period and offered a classification of the disease which has been generally accepted as simple and accurate. His work has been

instrumental in clarifying the clinical picture of lymphedema. The disease is divided into the noninflammatory and inflammatory types as follows:

A. Noninflammatory:
   1. Primary—
      a. Praecox.
      b. Congenital (Simple or Familial).
   2. Secondary—
      a. Malignant occlusion.
      b. Surgical removal of lymph nodes.
      c. Pressure.
      d. X-ray and radium therapy.

B. Inflammatory:
   1. Primary.
   2. Secondary—
      a. Venous stasis.
      b. Dermatophytosis.
      c. Systemic diseases.
      d. Local tissue injury or inflammation.

Noninflammatory Lymphedema

Lymphedema Praecox. This is the most common type of lymphedema. It affects young women in about 90 per cent of the cases. It may begin in childhood but most often appears during puberty. Painless swelling occurs in one lower extremity in the majority of cases, affecting the foot first and slowly progressing up the leg. The edema may remain mild, increase slowly or, rarely, rapidly involve the whole leg. Occasionally both legs are affected at the beginning, but more frequently the second leg is affected weeks to months after the first. The edema is soft at first, pits on pressure, and is more pronounced during warm weather and during menstrual periods. At the beginning it disappears when the patient retires and is increased by prolonged standing and walking. During this early period treatment is most effective and results in either control of the edema or prevention of progressive enlargement. In the absence of treatment and, in a few stubborn cases, the edema becomes intractable and the irreversible progression to elephantiasis makes the skin hard, rough, occasionally scaly and resistant to pressure. There is no pain but the limb becomes heavy and uncomfortable. In a small number of cases, 13 per cent in Allen's series, one or more attacks of acute lymphangitis occurs.

The cause of lymphedema praecox is unknown but because of its incidence in young women, its usual onset during puberty and its accentuation during pregnancy, it is believed that the female reproductive organs influence the etiology.

Congenital Lymphedema. Congenital lymphedema exists in two forms: (a) hereditary lymphedema, most commonly known as Milroy's disease, and (b) simple congenital lymphedema. Firm, diffuse edema is present at birth

and affects one extremity, usually a leg. The hereditary type is extremely rare and several members of the same family may be affected. Milroy originally reported the disease in 1892. In a follow-up report[4] in 1928, he had traced the disease through 6 generations of 42 persons. Twenty-two had lymphedema, 21 of whom had the condition at birth. Various reports of Milroy's disease have appeared in the literature, but in most cases the edema appeared in children or in young adults. Allen[2] feels that these incidents represent lymphedema of some other type, probably lymphedema praecox, with a family predilection.

Simple congenital lymphedema has been shown pathologically to be due to lymphangiectasis, by Middleton,[5] Allen,[6] and others. The picture is typical in that normal subcutaneous fat is replaced by large, dilated lymph spaces and fibrous tissues. There is no evidence of inflammation or thrombosis of lymph vessels or blood vessels. It is probable that the cause of the lymphangiectasis is a developmental anomaly.

Secondary Noninflammatory Lymphedema. Secondary lymphedema is due to a variety of causes. Most familiar is the surgical lymphedema of an upper extremity following radical surgery for carcinoma of the breast. Any condition producing lymphatic obstruction or destruction can result in lymphedema. Malignant disease is a common cause, either primary as in the lymphoma group, or from metastatic invasion of the lymph nodes by carcinoma originating in the breast, prostate, female pelvic organs, and probably other organs. For this reason it is of primary importance to eliminate any possibility of malignant disease by careful examination in all cases of lymphedema. Radiotherapy and extrinsic pressure on lymph channels have been reported to have caused secondary lymphedema.

Inflammatory Lymphedema

Inflammatory lymphedema is characterized by single or recurrent attacks of cellulitis and lymphangitis followed by varying degrees of chronic lymphedema. If more than one attack occurs there is an increase in the degree of edema following each attack until a far advanced, chronic lymphedema results. When the cellulitis and lymphangitis occur without an apparent precipitating cause, the resultant swelling is referred to as primary lymphedema. When it follows dermatophytosis, filariasis, pregnancy, and various systemic and localized infections, it is known as secondary lymphedema.

Whether primary or secondary, a typical attack occurs suddenly with chills, fever, malaise and occasionally nausea and vomiting. The temperature rises to 102 F. or higher and prostration is usually pronounced. A painful, tender, warm red area appears in the extremity and the lymph nodes draining the area become enlarged and tender. The process spreads until the entire limb is swollen, hot and tender. The fever continues for several days to a week and the acute inflammation in the leg slowly subsides within 1 to 2 weeks. There is residual swelling due to thrombosis of lymphatic vessels which is usually persistent and becomes more severe after each attack. The responsible organism

has been shown to be streptococcus. If only one attack occurs the lymphedema generally subsides slowly as collateral lymph channels are developed. The edema will become chronic, however, if it persists long enough for fibrosis and the resultant additional stasis to occur. Lymphedema often follows an infection or injury without any evidence of cellulitis or lymphangitis. Allen believes that the lymphatic infection in these cases is subclinical.

Diagnosis

Diagnosis of lymphedema is not often difficult. When the swelling is not severe and advanced skin changes have not occurred it must be distinguished from lipodystrophy. Both conditions occur more frequently in women and are similar in general appearance. The swelling of lipodystrophy is rather soft and spongy and either does not pit or pits slightly on pressure, and is always bilateral. Lymphedema is usually unilateral, is firmer in consistency and usually pits readily on pressure. Lipodystrophy is not progressive, does not disappear on rest and elevation of the legs, and occurs in obese women. Lymphedema is progressive and diminishes noticeably after a periodic elevation of the extremities. The advanced, chronic changes of lymphedema are characteristic, and are not seen in other conditions.

When bilateral, lymphedema must be distinguished from the edema caused by heart failure, kidney disease and hypoproteinemia, and when unilateral from chronic venous insufficiency and arteriovenous fistula. Acute lymphangitis may be confused with acute thrombophlebitis but the septic course and clinical evidence of lymphatic involvement is not observed in thrombophlebitis.

Treatment

The treatment of the early stages of lymphedema is generally satisfactory. It should be re-emphasized that the condition is not hopeless and the victim must not be allowed to become discouraged regarding the outcome. Treatment is exceedingly simple and if diligently pursued early in the disease will keep the edema at a minimum and prevent deformity. The patient should remain in bed, with the foot of the bed elevated to 10 to 12 inches, until the maximum reduction in size occurs. This may take only 2 or 3 days but occasionally a week is required. When there is no longer any decrease in the swelling the patient is provided with a well-fitted elastic stocking and allowed to be ambulatory. The stocking should be fitted only when the edema is at a minimum, preferably the first thing in the morning, and should always be put on before the patient gets out of bed. The limbs should never be dependent unless a good support is worn. Pure rubber roller bandages make an excellent support but because they are hot, cumbersome, and give a poor appearance most women refuse to wear them. Elastic stockings come in several weights and are made of either cotton or nylon; however they are fairly expensive and must be replaced several times a year. The patient should continue to sleep with the foot of the bed elevated. During the day the legs should be elevated at every opportunity. When the edema seems to be controlled the support may be

discontinued for a day or so but should be resumed if edema reappears and worn for another month before a further trial without support. Acute attacks of lymphangitis and cellulitis respond well to antibiotics which shorten the duration of the attack significantly. This treatment should be combined with the use of massive, hot, wet packs. In the primary type recurrent attacks are difficult to prevent but chronic infections, including dermatophytosis, should be eradicated if possible.

There is no satisfactory treatment for lymphedema following surgery for carcinoma of the breast, but occasionally elevation of the arm will reduce the swelling somewhat. The lymphedema caused by obstruction is usually the result of malignant disease and treatment should be directed toward the primary cause. In most instances the malignancy is far advanced, and except in rare cases of Hodgkin's disease and lymphosarcoma, which respond to radiotherapy or nitrogen mustard, treatment is merely symptomatic.

Surgical treatment of lymphedema is reserved for those far advanced cases of elephantiasis in which the extremity is massive in size, cumbersome and unsightly. The modified Kondoleon operation as advocated by Ghormley[7] and Pratt[8] is the procedure of choice. The subcutaneous tissue and fascia is completely removed so that the skin becomes attached to the muscle and the lymph is drained off through the muscle lymphatics. The limb can be reduced to normal size but the lymphedema recurs in a fairly large percentage of patients if an elastic support is not worn for an indefinite period postoperatively.

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EFFECT OF CHROMATES ON THE TEETH

A Comparative Report

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A DENTAL survey was made on 100 men employed in the chromate division of Diamond Alkali Company and the observations were compared with a similar number of Cleveland Clinic patients. The age range was comparable, the largest number of chromate workers falling in the 26 to 40 year old bracket, while the clinic group had the largest number in the 41 to 60 age group. The chromate group had no general complaints, while the patients in the clinic group had some systemic or oral disorder for which the dental inspection was requested.

In the chromate group, 79 reported or displayed evidence of irregular dental care. Such care had consisted primarily of extractions, as noted in the large number of missing teeth. Irregular professional care was noted in 55 of the 100 clinic patients.

In evaluating dental sepsis, x-ray evidence was a prime consideration. Teeth which showed periapical tissue change or excessive alveolar resorption extending beyond the middle half of the root of the tooth were classed as septic, and beyond conservative care.

In the chromate group a total of 30 (30 per cent) showed chronic dental sepsis, 17 per cent of which were diagnosed as chronic alveolar abscess; 10 per cent had severe periodontoclasia and 3 per cent displayed evidence of both conditions. Seventy per cent showed no definite chronic sepsis.

In the clinic group 58 per cent manifested conclusive indications of chronic dental focal infection. This might again be subdivided into 20 per cent with chronic alveolar abscess, 21 per cent having severe periodontoclasia and 8 per cent with both conditions. In the clinic group 42 per cent showed no evidence of chronic dental focal infection.

In the chromate group a total of 59 patients showed dental caries, of which 41 patients had widespread carious lesions while 18 had 2 or less. Twenty-four in this group revealed no dental caries. Seventeen were totally edentulous. In the clinic group 82 patients had dental caries and in 42 of these the condition was extensive. Seventeen of the patients had no dental caries. One was totally edentulous.

In the masticating function of the person under observation, the loss of one or more of the molar teeth (not considering the third molars), without replacement, was considered a deficiency. In the chromate group 74 showed evidence of masticating deficiency, as against 22 which were recorded as compensated. Four in this chromate group revealed normal masticating function without loss of any molar support.

In the clinic group, 80 revealed masticating deficiency. Ten were found to be adequately compensated, and another 10 possessed normal masticating function without loss of teeth. It should be added that 11 in this group had partial compensatory prosthesis in one or the other arch which had not, however, overcome the masticating deficiency in the opposite arch.

A study of the D.M.F. ratio (the relationship of decayed, missing teeth, and restorations [fillings]) revealed a ratio of 6 to 70 to 22 (table 1) from the chromate group which, interpreted, indicated that 6 of the group had more caries than missing teeth or restorations, 70 had a majority of missing teeth, while 22 had a majority of restorations (2 were not listed). In the clinic group 5 had a majority of caries, 44 a majority of missing teeth, while 57 had a majority of restorations. The age distribution of sepsis and caries in the two groups is shown in Table 2.

Summary

The clinic group had a higher incidence of dental caries (82 to 59), a higher incidence of masticating deficiency (80 to 74) and a lower incidence of masticatory compensation (10 to 22). This latter condition could be attributed to the higher occurrence of full dentures in the chromate group, which had the larger quotient of missing teeth (70 to 44).

The clinic group also showed a higher incidence of dental sepsis in comparison with the chromate group (58 to 30 per cent). Several factors might explain this situation. Clinic patients who had attempted conscientiously (higher incidence) to preserve teeth by restorations (51 to 22), manifested an increased pulpal mortality with complicating sepsis of those teeth. Abetting this conservative treatment, the factor of the greater number in the older age group of the clinic patients must be considered also. Furthermore, because of the disturbance caused by a situation in a group supposedly receiving more adequate dental service and having, paradoxically, a higher incidence of caries, sepsis and dental masticating deficiency, the clinic group was examined in comparison with the regular and irregular dental service groups (44 to 55). It was found that the clinic patients who were considered as having received regular dental service manifested 43 per cent of dental sepsis and 79 per cent of dental caries; those whose dental service had been irregular showed 70 per cent dental sepsis and 85 per cent dental caries.

Conclusion

From this comparative study, one cannot state that the added hazard of working conditions had increased the incidence of dental caries, sepsis or other oral manifestations for patients exposed to chromates. Persons who were inclined to have teeth removed, rather than repaired, actually had a lower incidence of dental caries and sepsis than a comparative group of clinic patients. In the latter group disposed to have teeth repaired there appeared to be an unduly high incidence of dental sepsis.

TABLE 1

COMPARATIVE DENTAL SURVEY

	Sepsis				Caries			Masticating Function			Personal Oral Care		Professional Oral Care		Ratio
	None	Abscess	Pyorrhea	Both	None	Slight	Severe	Normal	Compensated	Deficient	Regular (Daily)	Irregular	Regular (Annual)	Irregular	Decay Missing Fillings
Chromate Exposed Group 100 Men	70	17	10	3	24	18	41 a	4	22	74	35	58 b	19	79 c	6:70:22
Clinic Group 100 Men	42	29	21	8	17	40	42	10	10	80	48	51 d	44	55 e	5:44:51

a—Edentulous patients not included in this count.
b—Seven not listed.
c—Two not listed.
d—One not listed.
e—One not listed.

TABLE 2

SEPSIS AND CARIES BY AGE

	15 to 25 Age Group	26 to 40 Age Group	41 to 60 Age Group	61+ Age Group
Chromate Group (Sepsis)	7 in group 3 sepsis	56 in group 16 sepsis	34 in group 7 sepsis	6 in group 3 sepsis
Clinic Group (Sepsis)	8 in group 3 sepsis	27 in group 15 sepsis	58 in group 37 sepsis	5 in group 3 sepsis
Chromate Group (Caries)	7 in group 7 caries	56 in group 38 caries	34 in group 13 caries	6 in group 2 caries
Clinic Group (Caries)	8 in group 7 caries	27 in group 24 caries	58 in group 45 caries	5 in group 4 caries

I gratefully acknowledge the interest and cooperation of T. F. Mancuso, M.D., Chief, Industrial Hygiene Division, Department of Health, State of Ohio, through whose office and efforts this dental survey was made possible.

BERYLLIUM SKIN GRANULOMAS FROM A BROKEN FLUORESCENT TUBE

Report of a Case

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AS there are a large number of beryllium phosphor fluorescent lamp tubes still in use it is important to recognize and, if possible, prevent the specific chronic skin granuloma which can result from lacerations sustained in breaking these tubes. As in the previously reported cases of Grier,[1] Coakley,[2] Nichol,[3] and their co-workers, the following instance resulted from cuts inflicted by a fluorescent lamp tube in which the phosphor was a compound of zinc beryllium silicate, manganese and small amounts of finely divided and dispersed mercury. We have been informed that the fluorescent industry has ceased production of the beryllium containing phosphor.

Van Ordstrand et al.[4,5] have reported a rather extensive series of dermal lesions of different character occurring in workers extracting beryllium compounds from the ore. We are impressed in this case with the similarity of the microscopic picture of granuloma following fluorescent tube cuts to that observed at necropsy in our cases of chronic pulmonary granulomatosis[6] in persons exposed to beryllium and/or its compounds.

Case Report

A white man, aged 29, was seen on May 13, 1948, because of relatively painless lesions on the thumb, index and middle finger of his left hand. He stated that these were the sequelae of lacerations from a fluorescent tube which had exploded in his hand without apparent cause 6 months previously. He described the original wounds as having healed by primary intention without sutures. However, they were followed in several weeks by the local unsightly "overgrowth" of tissue resembling small tumors at the site of previous injury. The size of the lesions had attained a static level when seen. He had obtained several professional opinions on keloid reaction and had received a course of x-ray treatment without alteration in the lesions.

The physical examination proved essentially normal except for the skin lesions on his fingers as shown in the photograph (fig. 1a). The attendant laboratory studies (which included blood counts, urinalysis, blood sugar, sedimentation rate and blood serology) were all negative or within normal limits as was an x-ray examination of his chest.

Particularly because of this history of antecedent fluorescent tube injury a tentative

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diagnosis of chronic beryllium skin granuloma was made. The lesions on the dorsum of the middle finger and on the index finger were excised on May 18, 1948.

The third lesion (on thumb) has not been excised as the patient desires to observe the ultimate scientific outcome. In nearly 1½ years' observation by us the lesion has remained unchanged. Neither of the two excised areas has shown signs of recurrence after a similar lapse of time (fig. 1b).

Pathology

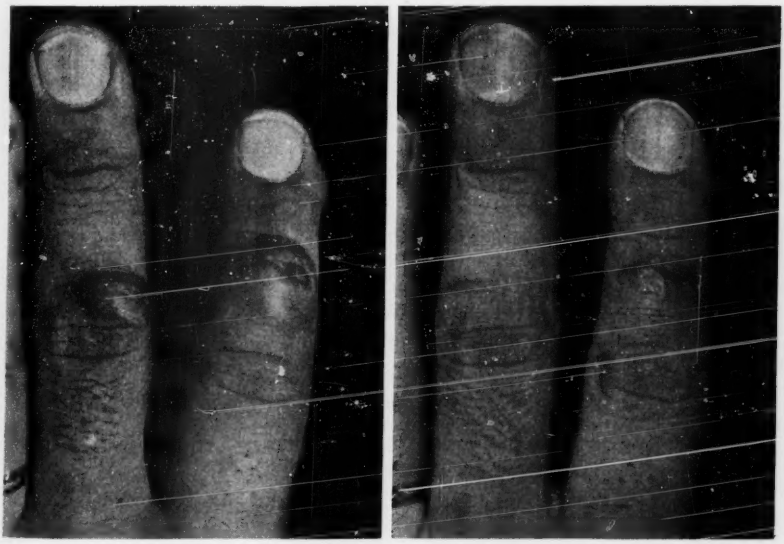
In the opinion of the pathologist,[7] the granulomatous reaction was identical to that observed in chronic pulmonary granulomatosis in beryllium workers, and compatible with the effects of beryllium phosphor. Two other authorities[8,9] reviewed the histopathology and concurred in this opinion.

The pathologic diagnosis was interpreted as follows:

GRANULOMA, SKIN. Consistent with beryllium granuloma (fig. 2).

Gross: The specimen consists of an ellipse of skin, 2.5 x 1.0 x 0.5 cm., the central portion of which is slightly and irregularly raised and finely nodular. The surrounding skin is unusually hard. On section, the corium beneath the altered epithelium is replaced by firm, almost homogeneous gray tissue.

Microscopic: The corium throughout the thin lining of the specimen reveals frequent focal accumulations of histiocytes, of epitheloid type and in



(a) (b)

FIG. 1. (a) Gross appearance of granulomata prior to surgical excision. (b) Fingers of patient showing no granulomatous recurrence 1½ years after excision of lesions. The third and unremoved granuloma exhibits no change.

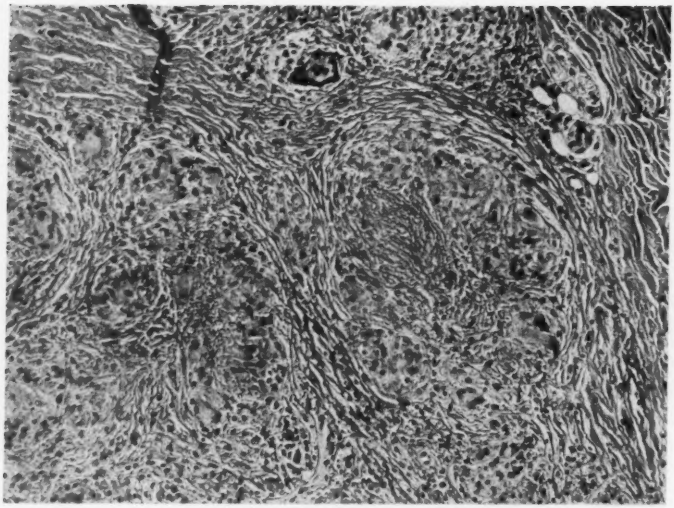


Fig. 2. Histopathology of one of excised skin lesions showing typical granulomatous changes in the corium.

these foci occasional rather large giant cells of foreign body type. In addition to these tubercle-like lesions there are several broad patches of necrosis with fibrinoid material present. A moderate number of lymphocytes are present about some tubercles.

Comment

In a patient presenting "keloid-like" lesions following old fluorescent lamp tube cuts the possibility of beryllium granuloma should be considered. These lesions might possibly be circumvented with early and complete debridement of the accompanying lacerations. Of utmost importance is the prevention of lacerations from careless handling of old fluorescent lamp tubes, inasmuch as a considerable number of tubes manufactured with beryllium phosphor remain in use or in stock.

Summary

1. Chronic beryllium skin granuloma can follow laceration from a fluorescent lamp tube manufactured with beryllium phosphor.

2. The histopathologic diagnosis of lesions in the case presented is similar to that of chronic pulmonary granulomatosis observed in persons exposed to beryllium and/or its compounds.

3. Observations on this specific traumatic beryllium granuloma indicate that it does not have migratory properties and is cured by local surgical excision.

4. It is possible that similar lesions might be prevented by thorough cleansing and debridement at the time of the laceration.

5. Prevention of fluorescent lamp tube cuts is extremely important as old tubes containing beryllium phosphor are still in use and considerable stock remains. We are informed that the fluorescent industry has discontinued the manufacture of tubes with beryllium phosphor.

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THE DIAGNOSIS AND TREATMENT OF ACUTE AGRANULOCYTOSIS

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PROMPT recognition of acute agranulocytosis is important because early and adequate treatment will effect a complete recovery in about 90 per cent of the patients. Penicillin, and to a lesser extent other antibiotics and chemotherapeutic drugs, have reduced materially the former high mortality rate.

The severity of the disease is demonstrated by the initial report of Schultz[1] in 1922 in which 5 fatal cases were described, each characterized by extensive ulcerations of the mouth and pharynx, fever, and a pronounced decrease of the white blood cell count. He observed the profound diminution of the polymorphonuclear leukocytes and the total absence of these cells from the peripheral blood and suggested the name agranulocytosis. This report created world-wide interest and recognition of the clinical syndrome although Brown[2] in this country is credited with the first authentic case report in 1902.

The term "agranulocytic angina" was introduced in 1923 and is generally accepted. Some of the more common synonyms include malignant leukopenia, granulopenia, and toxic myelosis. The latest edition (1942) of the Standard Nomenclature of Diseases of the American Medical Association recommends the name "acute agranulocytosis" under the inclusive term granulocytopenia.

Clinical Manifestations

The onset of the disease is usually abrupt but may be preceded by headache, malaise or mild prostration for 1 or 2 days. It has been shown that depression of the white blood cell count due to a decrease in the granulocytes occurs prior to the onset. The symptoms are usually sore throat, difficulty in swallowing, and fever indicative of infection. The physical examination reveals an acutely ill patient with temperature ranging from 101 F. to 103 F., rapid pulse, and often mild delirium. The oral mucous membranes including the fauces, gums, tongue, and pharynx show multiple superficial ulcerations covered with a tenacious brown exudate. The tonsils and other lymphoid tissue in the pharynx are red, swollen, and may show evidence of necrosis. Cervical lymphadenopathy is frequently observed although generalized lymphadenopathy is absent. The spleen is rarely palpable. The liver is seldom enlarged but jaundice may occur in critically ill patients as a result of the severe infection and is generally a deterrent to recovery. If unusual pallor is observed suggesting an anemia, some doubt must be entertained concerning the accuracy of the diagnosis.

Etiology

In 1932, Kracke[3] reported the production of a severe granulocytopenia in rabbits receiving subcutaneous injections of benzene in olive oil. He stated that the cause of acute agranulocytosis was unknown but that the benzene ring must be given strong consideration. Madison and Squier[4] in 1934 conclusively demonstrated that amidopyrine was the cause of the disease in 14 patients. They were able to show a prompt and temporary depression of the granulocytes following the oral administration of 0.3 Gm. of amidopyrine to 2 patients who had recovered from the disease. These facts were later confirmed by others.

Arsphenamine and neoarsphenamine may cause acute agranulocytosis but more often these drugs produce a toxic marrow depression with anemia, leukopenia and thrombopenia. Fortunately, these reactions were uncommon except during the era of rapid arsenotherapy. Shortly after the introduction of the sulfonamide drugs, it was established that agranulocytosis may follow the use of sulfanilamide, sulfapyridine, sulfathiazole, sulfadiazine and sulfamerazine. Even sulfaguanidine and succinyl sulfathiazole, which are absorbed poorly from the gastrointestinal tract, can cause this disease. This observation is of interest in view of the experimental production by Daft[5] of a profound granulocytopenia in rats fed a purified diet and succinyl sulfathiazole successfully treated with folic acid. Theoretically, it is believed that the synthesis of folic acid in the intestinal tract is impaired by the alteration of the bacterial flora resulting from the succinyl sulfathiazole.

Gold, widely used in the treatment of rheumatoid arthritis, is another therapeutic agent capable of causing agranulocytosis. However, such reaction is uncommon. Toxic reactions are more apt to occur as high total dose levels are approached. Dinitrophenol was soon withdrawn from the accepted drug list because of this and other toxic effects. To date, no convincing reports have been published on tridione or mesantoin as causes of agranulocytosis. These new anticonvulsant drugs are not without toxic effects however as several reports have confirmed the production of an aplastic anemia following their use. Within the past year, 2 patients have been observed at the Cleveland Clinic Hospital with anemia, leukopenia, and hypoplastic bone marrow due to mesantoin. Both recovered.

With the advent of the antithyroid drugs it became evident that thiouracil, methyl thiouracil, and propyl thiouracil were capable of producing agranulocytosis. Thiouracil is considerably more toxic in this respect than the later derivatives. Propyl thiouracil and methyl thiouracil rarely give rise to a serious granulocytopenia if excessively large doses are not employed. In a group of 450 patients treated with propyl thiouracil at the Cleveland Clinic, none developed agranulocytosis.[6]

The following drugs have been suspected of causing agranulocytosis but conclusive proof is lacking: barbiturates, phenacetin, quinine and quinidine, cincophen, bismuth, and plasmoquin.

Blood and Marrow Observations

There may be a mild anemia of a normochromic or hypochromic type but if any appreciable reduction of the hemoglobin, red blood cell count, or platelets is present, the accuracy of the diagnosis is questionable. The characteristic feature is a severe depression of the total white blood cell count (leukopenia) with a relative decrease of the polymorphonuclear leukocytes (granulocytopenia). The lymphocytes and monocytes show no consistent change in number nor morphology. The granulocytes are usually below 20 per cent, often 10 per cent, and not infrequently they may be entirely absent. The granulocytes often show basophilic granulation which is considered a toxic effect. Repeated blood counts are important in order to record the progress of the patient. A significant increase of granulocytes in the peripheral blood often indicates a clinical recovery may be expected. (These features are noted in the series observed at the Cleveland Clinic—Table).

Following observation of the bone marrow changes in several fatal cases Fitz-Hugh and Krumbhaar[7] proposed the concept of a maturation arrest of the granulocytic cells at the myelocyte stage of development. Others have confirmed by sternal puncture technic the presence of ample granulocytic cells up to and including myelocytes, and the virtual absence of metamyelocytes and mature granulocytes. The observations vary according to the stage of the disease but myeloid hyperplasia is recognizable during the acute phase. There is no disturbance of erythropoiesis and the megakaryocytes appear normal.

Case Reports

Case 1. A 29-year-old physician consulted Dr. Russell Haden[8] in December, 1933, and gave a history of recurring attacks of chills, fever, stomatitis, and pharyngitis. In each attack a leukopenia with relative decrease in the granulocytes was observed. The first episode occurred in September, 1932, and during the ensuing 15 months, he had 8 recurrent attacks. Further history revealed that these attacks were preceded by migraine headaches from which relief was sought by the use of amidopyrine, 0.6 to 0.9 Gm. (pyramidon), allonal (containing amidopyrine), and acetylsalicylic acid. Repeated blood counts showed no evidence of anemia. The total white blood cell count varied from 1500 to 3000 per cu. mm. with the polymorphonuclear leukocytes comprising 4 to 15 per cent. All drugs containing amidopyrine were stopped and no further attacks recurred during the following 4 years, while subsequent blood counts have remained normal.

Case 2. A 48-year-old salesman was referred to the Cleveland Clinic on June 21, 1949, with the chief complaint of sore throat. The present illness began abruptly 10 days prior to admission, characterized by sore throat, fever, and swollen cervical glands. During the 6 days prior to admission, he received daily injections of 300,000 units of penicillin without appreciable clinical improvement and his fever and stomatitis continued. No blood counts were performed prior to admission. The past history disclosed that a diagnosis of diffuse toxic goiter and coronary heart disease had been established in 1947. Treatment at that time was started with thiouracil, 0.9 Gm. daily, in repeated courses of 2 to 3 weeks' duration. The last course was instituted 2 weeks prior to the onset of the present illness and several tablets were prescribed the day before admission to the Clinic.

TABLE

TABLE

Age	Sex	Total W.B.C. Count	P.M.N. (%)	R.B.C. Million Per Cu.Mm.	Hb. %	Drug	Treatment	Result
65	M	400	4	3.86	65	Allonal Aminopyrine	Transfusion Pentnucleotide	Died
59	F	750	4	4.2	78	?	Transfusion Liver extract	Recovered (several attacks)
68	F	2650	0	4.8	75	Sulfathiazole	Transfusions Penicillin Liver extract	Recovered
48	M	2050	20	4.7	94	Thiouracil	Penicillin Streptomycin Liver extract Folic acid	Recovered
46	F	250	10	4.55	68	Aminopyrine	Transfusions Liver extract	Recovered
52	F	600	0	4.0	80	?	Transfusions	Died
29	M	2200	8	4.6	95	Aminopyrine	Pentnucleotide Transfusion Liver extract	Recovered (several attacks) Migraine
59	F	1200	12	4.9	84	Aminopyrine	Sulfathiazole	Recovered

Physical examination revealed an acutely ill patient with a fever of 102.2 F., pulse of 120, and a thick gray exudate over the oral mucous membranes and pharynx beneath which multiple small ulcerations were observed. The tonsils showed several necrotic ulcers. The cervical lymph nodes were enlarged and tender but there was no generalized lymphadenopathy. There was no icterus, purpura, nor dermatitis. The liver and spleen were not palpable. The previous clinical diagnoses of diffuse toxic goiter and coronary heart disease were confirmed by later studies.

On admission, the hemoglobin was 14.5 Gm., red blood cell count 4,730,000 per cu. mm., white blood cell count 1500 per cu. mm., with 20 per cent granulocytes, 66 per cent lymphocytes, and 14 per cent monocytes. Most of the granulocytes were mature although several myelocytes and metamyelocytes were observed. The polymorphonuclear leukocytes showed severe basophilic (toxic) granulation. Sternal puncture disclosed a cellular marrow with normal erythrogenesis and myeloid hyperplasia. The striking feature was the noticeable increase of myelocytes and conspicuous reduction of mature granulocytes. Blood cultures remained sterile. Other studies, including roentgen examination of the chest, were normal.

The initial procedure in treatment was the cessation of thiouracil. The penicillin was continued and increased to 600,000 units daily. Dihydrostreptomycin, 1 Gm. daily, in divided doses was given parenterally until recovery 7 days later. In addition, he received 6 cc. of liver extract intramuscularly and parenteral crystalline folic acid in 10 mg. doses three times each day. The stomatitis and pharyngitis gradually improved and he was afebrile on the seventh hospital day. Prior to discharge, the white blood cell count was 12,250 per cu. mm. with 70 per cent granulocytes. His convalescence was uneventful and radioactive iodine was advised for the treatment of his hyperthyroidism.

The patient was seen in the later stage of acute agranulocytosis and it appears that the empiric use of penicillin prior to recognition of the diagnosis prevented a fatal result in spite of continuation of the thiouracil.

Differential Diagnosis

Agranulocytosis is a brief illness with an acute onset occurring primarily in adults. The stomatitis, pharyngitis, and mucosal ulcerations are also present in such conditions as acute leukemia, acute aplastic anemia, diphtheria, Vincent's angina and other local infections. Characteristic changes in the peripheral blood and bone marrow in agranulocytosis have been discussed. It is usually possible to obtain a history of the use of some drug capable of causing the disease prior to the acute onset. In general, the absence of generalized lymphadenopathy, splenomegaly, pallor, or purpura aid in the differential diagnosis of acute agranulocytosis.

The conditions most likely to present difficulties in the differential diagnosis are acute leukopenic leukemia and acute toxic aplastic anemia. In these diseases, anemia and thrombopenia are seldom absent. In leukopenic leukemia, careful study of the blood smears will reveal the presence of "blasts." This study is facilitated by preparation of a concentrated smear of the "buffy coat" from the hematocrit tube which contains primarily the white blood cells. Bone marrow studies obtained by sternal or iliac crest puncture often give conclusive proof of the diagnosis in these diseases.

Treatment

The prevention of acute agranulocytosis is perhaps possible to a limited extent but is difficult in view of the abrupt onset. The physician's awareness of the various drugs capable of producing this reaction is important. It has been shown that only a small percentage of patients develop this complication as a result of these drugs. There appears to be no adequate explanation for the infrequent observation of acute agranulocytosis during the period 1902 to 1925, as pyramidon (amidopyrine) was widely used following its introduction from Germany in 1902. There is no convincing evidence that allergy plays a role. The reaction appears to be a drug sensitivity in susceptible persons.

In the clinical use of the sulfonamides and antithyroid drugs which are administered daily over a period of time, instruction of the patient to report promptly any symptom indicative of this complication is probably the most important feature in its prompt recognition. Progress blood counts may be of some value depending on the relative toxicity of the drug employed. With the constant influx of new drugs on the market, the possibility of granulocytopenia should be kept in mind as these reactions may not have been observed in animal experiments nor preliminary clinical trials. For example, Blanton and Owens[9] recently reported a case of acute agranulocytosis in an elderly woman receiving 200 mg. of pyribenzamine daily for the treatment of urticaria. They believed this was the offending agent but hesitated to administer the drug in a clinical trial following the recovery of the patient. Additional evidence is presented that pyribenzamine may cause agranulocytosis by the case report of Cahan and his associates.[10] They cite personal knowledge of a similar reaction to this antihistaminic drug. In these 3 patients the drug was taken for several weeks prior to the onset of the agranulocytosis.

As soon as the diagnosis of acute agranulocytosis is established or strongly suspected, the offending drug should be determined and its administration stopped. Vigorous measures for the control of the infection are essential and since the advent of penicillin, it is the agent of choice. It is suggested that minimal parenteral doses of 600,000 units be given daily until the patient recovers. Depending on the clinical condition of the patient and bacteriologic studies, streptomycin, chloramphenicol, or aureomycin may be required as supplementary measures.

Sulfonamide drugs, especially sulfadiazine, were often effective in controlling the infection but have been largely replaced by the less toxic antibiotics. In the treatment of agranulocytosis due to the heavy metals such as gold or arsenic, the use of BAL is recommended in conjunction with agents to control infection.

Conservative treatment of the oral lesions is advisable and consists of warm saline irrigation and applications of mild antiseptics. The topical application of penicillin to the mucous membranes is of dubious value.

Blood transfusions may be useful in correction of mild anemia and as a general supportive measure. There is little proof that the transfused leukocytes cause more than a transient rise in the white blood cell count of the recipient.

If transfusions are given, whole freshly drawn blood is probably better than "banked" blood.

It is believed that a large percentage of patients will recover if the infection is effectively controlled during the period of granulocytopenia which often lasts for 5 to 8 days. The return of granulocytes in the peripheral blood is apparently spontaneous. In view of the experimental evidence in animals that granulocytopenia due to the sulfonamides and antithyroid drugs is benefited by folic acid, this agent has been advocated and generally used in recent years. Theoretically, it appears sound to give 10 to 20 mg. of folic acid parenterally several times daily, although clinical proof of its exact value is difficult to establish.

Pentnucleotide therapy is not recommended.

Summary

The clinical and hematologic features in acute agranulocytosis have been discussed and the present concept of treatment outlined.

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THE FRANK E. BUNTS EDUCATIONAL INSTITUTE

A continuation course will be presented on
Thursday, Friday, and Saturday, April 6, 7, and 8, 1950

PRACTICAL PROBLEMS IN GENERAL SURGERY

Tentative Program

Thursday, April 6, 1950

8:00-9:00 a.m.	Registration.
9:00 a.m.	Fluid and Electrolyte Balance in the Surgical Patient — A. C. CORCORAN, M.D.
9:30 a.m.	Protein Metabolism and Nutritional Problems in the Surgical Patient — STANLEY O. HOERR, M.D.
9:50 a.m.	Principles of Healing and Management of Complicated Wounds — GEORGE CRILE, JR., M.D.
10:10 a.m.	Intestinal Intubation — A. H. ROBNETT, M.D.
10:30 a.m.	Intermission.
10:40 a.m.	Management of Pulmonary Complications — DONALD B. EFFLER, M.D.
11:00 a.m.	Safeguards of Anesthesia — DONALD E. HALE, M.D.
11:20 a.m.	The Heart in Relation to the Risk of Operation — A. CARLTON ERNSTENE, M.D.
11:40 a.m.	Changes in Coagulation of Blood in Surgical Patients — WILLIAM D. HOLDEN, M.D.*
12:20 p.m.	Questions and Discussion.
12:30 p.m.	Luncheon—Courtesy of Cleveland Clinic.
1:50 p.m.	Appendicitis and Peritonitis — GEORGE CRILE, JR., M.D.
2:10 p.m.	Management of Retention of Urine and Infections of the Urinary Tract — WILLIAM J. ENGEL, M.D.
2:30 p.m.	Relief of Pain in Incurable Cancer — W. JAMES GARDNER, M.D.
2:50 p.m.	Parietal Pain Simulating Intra-Abdominal Disease — EDWARD C. WEIFORD, M.D.
3:10 p.m.	Present Status of Radiation Therapy in the Treatment of Cancer — U. V. PORTMANN, M.D.
3:30 p.m.	Intermission.

3:50 p.m.	Abdominal Pain Due to Disease of the Genitourinary Tract	CHARLES C. HIGGINS, M.D.
4:10 p.m.	Tendon Surgery in the Hand	GEORGE S. PHALEN, M.D.
4:30 p.m.	Primary Tumors of the Neck	ROBERT S. DINSMORE, M.D.

Friday, April 7, 1950

8:30 a.m.	Antithyroid Drugs in the Treatment of Hyperthyroidism	E. P. MCCULLAGH, M.D.
8:50 a.m.	Radioactive Iodine in the Treatment of Hyperthyroidism	CHARLES RICHARDS, M.D.
9:10 a.m.	Surgical Treatment of Hyperthyroidism	ROBERT S. DINSMORE, M.D.
9:30 a.m.	Simple Goiter, Thyroiditis and Cancer of the Thyroid	GEORGE CRILE, JR., M.D.
10:00 a.m.	Discussion.	
10:10 a.m.	Intermission.	
10:20 a.m.	Cancer of the Lung	DONALD B. EFFLER, M.D.
10:40 a.m.	Problems of Anorectal Surgery	RUPERT B. TURNBULL, M.D.
11:00 a.m.	Ulcerative Colitis and Regional Enteritis	E. N. COLLINS, M.D.
11:20 a.m.	Special Problems in Fractures	JAMES A. DICKSON, M.D. and JAMES I. KENDRICK, M.D.
12:20 p.m.	Questions and Discussion.	
12:30 p.m.	Luncheon—Courtesy of Cleveland Clinic.	
1:30 p.m.	Bleeding from the Gastrointestinal Tract	STANLEY O. HOERR, M.D.
2:00 p.m.	Surgery of the Spleen	ROBERT S. DINSMORE, M.D.
2:30 p.m.	Tumors of Oral Cavity and Salivary Glands	GEORGE CRILE, JR., M.D.
2:50 p.m.	Surgery of the Esophagus	DONALD B. EFFLER, M.D.
3:30 p.m.	Intermission.	
3:50 p.m.	Tumors of the Breast	ROBERT S. DINSMORE, M.D. and A. H. ROBNETT, M.D.
4:10 p.m.	Principles of Skin Grafting and Treatment of Burns	DONALD M. GLOVER, M.D.**

SYMPOSIUM

8:15 p.m.	Vascular Surgery	Drs. Daniel C. Elkins,† Claude S. Beck,‡ and Rupert B. Turnbull with A. Carlton Ernstene as moderator

Saturday, April 8, 1950

8:30 a.m. . . . Pitfalls in Roentgen Diagnosis of the Gastrointestinal Tract . . . . . C. ROBERT HUGHES, M.D.

PANEL DISCUSSIONS

9:00 a.m. . . . Surgery of the Colon . . . Drs. George G. Finney,\$ George Crile, Jr., R. B. Turnbull, and S. O. Hoerr with D. C. Elkin as moderator

10:00 a.m. . . . Surgery of the Pancreas and Biliary Tract . . . . Drs. G. G. Finney, George Crile, Jr., and S. O. Hoerr with R. S. Dinsmore as moderator

11:00 a.m. . . . Surgery of the Stomach and Duodenum . . . . . Drs. G. G. Finney, George Crile, Jr., and E. N. Collins with S. O. Hoerr as moderator

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**Assistant Professor of Surgery, Western Reserve University.*

***Associate Clinical Professor of Surgery, Western Reserve University.*

†Professor of Surgery, Emory University.

‡Professor of Neurosurgery, Western Reserve University.

\$Assistant Professor of Surgery, Johns Hopkins University.

REGISTRATION BLANK

THE FRANK E. BUNTS EDUCATIONAL INSTITUTE ....., 1950
Cleveland Clinic Building
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Please register me for the course on "Practical Problems in General Surgery" which is to be given April 6, 7 and 8, 1950. (Registration Fee is $15.00.)

I am enclosing check for $5.00 and the remainder will be paid on Registration, April 6.

NOTE: Checks should be made payable to the Frank E. Bunts Institute. Mail registration blank and check to Dr. Edwin P. Jordan, Cleveland Clinic Building, 2020 East Ninety-third Street, Cleveland 6, Ohio.

Name .....

Address .....

Medical School and date of graduation .....

This course is open only to graduates of approved medical schools. Registration will be limited to the number of physicians who can be adequately accommodated.

APPOINTMENTS

On January 1, Dr. Stanley O. Hoerr joined the staff of the Department of General Surgery. Dr. Hoerr received his M.D. degree from Harvard University Medical School in 1936, following which he served successively as intern, assistant resident in surgery, and chief resident in surgery at the Peter Bent Brigham Hospital in Boston. From 1942 to 1945 he served with the 5th General Hospital, E.T.O. and at the close of the war was assistant chief of surgery with that unit. He then returned to Harvard where he was instructor in surgery. In 1947 Dr. Hoerr went to Columbus, Ohio, where he was attending surgeon at the Ohio State University Hospital and associate professor of surgery. Dr. Hoerr, who specializes in abdominal surgery, was certified by the American Board of Surgery in 1946. He is the author of a number of contributions to the surgical literature and a member of numerous surgical societies.

Dr. Donald B. Effler has been appointed to the staff in the Department of Thoracic Surgery. Dr. Effler was graduated from the University of Michigan in 1937 and received the M.D. degree from that institution in 1941. Following his internship at Mercy Hospital in Toledo, Dr. Effler served residencies at Walter Reed General Hospital, Gallinger Municipal Hospital in Washington, D. C., and at the Hospital of the Good Samaritan in Los Angeles. He was Adjunct Clinical Professor of Surgery at George Washington University from 1947 to 1948. Dr. Effler spent five years in the medical corps of the U. S. Army. He has published a number of articles principally in the field of thoracic surgery.

Dr. Robert E. Wise has been appointed a member of the staff in the Department of Roentgenology. Dr. Wise attended the University of Pittsburgh and graduated from the University of Maryland School of Medicine in 1943. He served with the U. S. Navy for four years, receiving his internship at U. S. Naval Hospital in Philadelphia. In 1947 Dr. Wise was granted a two year fellowship at the Cleveland Clinic and was made a staff assistant in 1949. He has been certified by the American Board of Radiology.

BUNTS LECTURE

The Frank E. Bunts Educational Institute has scheduled the following Bunts lecture on January 23, 1950. This lecture will be held at the Cleveland Clinic at 8:15 p.m. Visitors are cordially invited.

January 23, 1950—Dr. A. C. Ivy.

Physiology of the Stomach and Peptic Ulcer.

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UREMIA*

LOUIS LEITER, M. D.
Clinical Professor of Medicine, Montefiore Hospital, New York

ORIGINALLY uremia signified the end stage of organic renal disease when urea was demonstrable in the serum. This was Bright's concept[1] based on the chemical analyses of Christison. Although it was later shown that the blood normally contained urea and that excessive urea concentration could not by itself reproduce the complex manifestations of uremia, the term "uremia" nevertheless became permanently rooted in medical texts and no one would think seriously of displacing it. Probably one of the chief reasons for this was the complete failure throughout the last hundred years to demonstrate any single metabolite or toxin the retention of which could be responsible for uremia. Each of the normally present urinary constituents has been shown to be capable of producing one or more of the major symptoms of the uremic state. But none has met the rigid scientific tests of (1) reproduction of the general state of uremia, (2) effectiveness in causing important symptoms at or near the concentration of the substance in the blood in natural uremia (Table 1).

For example, **ammonium** salts were implicated early in the etiology of uremia.[2] Intravenous injection of ammonium salts produces hyperpnea, convulsions, coma and death. The urine in the end stages of renal disease contains little ammonia, if bacterial infection or contamination is excluded, suggesting that ammonia is retained in the blood. Yet it took another 70 years before Nash and Benedict[3] showed that there is practically no ammonia in normal blood and no increase in uremic blood. In fact, the ammonia normally excreted in the urine is manufactured by the kidney itself – and the failure to produce it during renal insufficiency is a major factor in the **acidosis** of uremia.

Table 1

THEORIES OF UREMIA

1. Retention of urinary solutes
   a) Organic – urea, guanidines, phenols
   b) Inorganic – ammonium, potassium, phosphate, sulfate, chloride, water
2. Toxic effects of renal autolysis
3. Metabolic disorganization
4. Lack of normal renal products

This paper is slightly abridged from a wire recording of a lecture given November 19, 1949, in connection with the Bunts Institute course on Disorders of the Urinary Tract.

What about **urea?** It rises to enormous levels in the blood and all body fluids in uremia; it produces nausea, vomiting, headache, dizziness, diarrhea, twitchings, stupor and coma on intravenous injection into normal animals. Many investigators, including the writer,[4] some 30 years ago, were seriously impressed by the analogy to natural uremia and attributed differences between the artificial and natural variety to the time element or the rate of accumulation. However, it was not realized at that time that the intravenous injection of any strongly hypertonic solution—whether of urea, sodium chloride or other electrolytes, sucrose, even glucose and alcohol—would by its excretion and resultant severe dehydrating action produce all of the symptoms described. If urea were administered more carefully, high blood levels could be achieved with practically no uremic symptoms. Furthermore, patients with high blood urea levels as a result of renal impairment often show few if any signs of clinical uremia; on the contrary, uremic symptoms may persist long after the blood urea level has been lowered into the normal range by vigorous therapy. However, we have learned, incidentally, from the experiments with urea and other hypertonic solutions that **dehydration,** if acutely produced, can cause symptoms that closely simulate some of the major manifestations of full-blown uremia, including elevations of blood urea.

How about **potassium?** No one would seriously blame uremia on potassium retention nowadays but it might well be the immediate cardiac cause of death, especially in anuric individuals with acute nephritis or toxic nephrosis, in untreated or poorly treated Addison's disease, in crisis, and in the traumatic crush syndrome. Addis and Lew,[5] Bergman and Drury[6] neatly established potassium as the lethal factor in high meat diets when fed to nephrectomized or acutely renal-insufficient rats. Potassium may be increased to dangerous concentrations in uremia; on the other hand, in some few cases it may be reduced by vomiting, diarrhea or diuresis to critically low levels in the serum. The conclusion is that, in addition to acidosis and dehydration, **specific eletrolyte disturbances** play a role in uremia (Table 2).

In uremia, the serum **calcium** level is reduced often due to retention of inorganic phosphate. Tetany may occur but ordinarily is counteracted by the increased ionization of calcium, secondary to acidosis, and the depression of the neuromuscular system by other factors in uremia. The muscular twitchings so common in advanced uremia are apparently not related to serum calcium. Convulsions in uremia are rarely to be attributed to low serum calcium ions. One must also consider the opposite situation – hypercalcemia which may result from parathyroid or bone disease of various types, from vitamin D overdosage, rarely from excessive ingestion of milk and alkalis in the management of peptic ulcer. In all of these conditions, a state closely resembling uremia may supervene even in persons with previously normal kidneys.

The story of **chloride** in uremia is also one of ups and downs, so that one may speak of hypochloremic azotemia or hyperchloremic uremia. There

Table 2

DIAGNOSIS	BLOOD	SERUM						BLOOD
	Urea N.	Na	Cl	CO_2	K	Ca	P	Creatinine
	mg.%	meq/1	meq/1	meq/1	meq/1	mg.%	mg.%	mg.%
Chronic Nephritis	75	145	*115*	*15*	5	8	*8*	6
Pyelo-nephritis	75	130	*85*	25	4	8	8	8
Peptic Ulcer	75	135	*75*	*45*	*3*	10	5	3
Adrenal Failure	75	*120*	85	20	*7*	10	4	4
Anuric Nephrosis	75	135	85	20	*7*	*7*	*12*	9
Ca of Breast + Testosterone	75	135	95	25	5	*16*	*7*	4
Gastro-enteritis	75	*180*	*145*	15	*3*	12	*7*	6
Enlarged Prostate	75	150	*120*	*15*	5	9	6	*3*
Normal	15	145	105	30	5	10	4	1

The variability of electrolyte levels in different types of uremia. For the sake of simplicity, the figures for Na, Cl and CO_2 are given to the nearest 5 meq.

are many reasons why the serum chloride concentration may be reduced greatly in uremia – vomiting, diarrhea, loss in dilute urine, shift from extracellular to intracellular fluids, dilution of available chloride by excess water intake and edema formation, low intake, displacement of chloride ion by retained sulfate ion, ketone acids, lactic acid and other organic anions. The serious symptoms associated with hypochloremia are due largely to the coexistent complex metabolic disturbances. Hyperchloremia in uremic states usually results from over-treatment of acute anurias with saline solutions. Sodium chloride, with its ion ratio of chloride to sodium of 1:1, contains excess chloride, since in extracellular fluids the ratio of chloride to sodium is only 2:3. The normal kidney easily takes care of this discrepancy, but in severe renal impairment this is not the case and chloride retention with hyperchloremic acidosis results. Temporary hyperchloremic acidosis has often been produced unwittingly by physicians during vigorous saline infu-

sion treatment of diabetic ketosis, postoperative states and other conditions of dehydration or shock during periods of relative renal insufficiency.

The role of electrolytes in the syndrome of uremia has been recently strikingly demonstrated by Grollman and his associates.[7] They prolonged life in nephrectomized dogs by diets exceedingly low in sodium chloride, potassium, phosphate and sulfate but containing protein, fat and carbohydrate and water in balanced proportions.

Granting that the syndrome of uremia is to a large extent compounded of dehydration, acidosis and electrolyte disturbances, is there a **toxic organic metabolite** responsible for the resistant anemia, the central nervous symptoms, intractable nausea and pruritus? Many investigators have blamed guanidine or its derivatives and free phenolic compounds.[8] Some of these substances, like guanidine, increase neuromuscular irritability, others are potent depressants and could cause the apathy, stupor and final coma of uremia. No one can evaluate the true role of these substances chiefly because of the lack of specific analytic methods. There are also the autolytic products of slowly degenerating or acutely ischemic or anoxic kidney tissue. To the absorption of these many of the lesions and symptoms of malignant hypertensive uremia have been attributed, originally by Ascoli[9] and more recently by Winternitz et al.,[10] Leiter and Eichelberger[11] and Masson et al.,[12] in experiments with various renal or endocrine extracts. As yet too little progress has been made in the understanding of these products.

Much of the preceding discussion applies equally to organic renal uremia and to the vast group of prerenal or extrarenal azotemias (Table 3). Is there any basic difference between **renal uremia and prerenal uremia?** If nothing is known of the patient's previous history and condition and he is examined as of the moment, one would have great difficulty in distinguishing between the two kinds of uremia. The blood chemical changes may be comparable in the two groups. The urinary chemical changes may also be the same in the two although the urinary sediment may furnish differential diagnostic clues as to the underlying condition. The reason for these similarities is not surprising in view of the common electrolyte and fluid disturbances of prerenal azotemia and renal uremia. Furthermore, if prerenal disturbances last more than a few days, severe renal hypoxia and actual tubular degeneration combine to convert the original secondary renal dysfunction into an irreversible functional disorganization. In the acute uremias of prerenal origin there is always hope for restoration of function in a previously good kidney given an adequate blood supply and a decent fluid environment. The more damaged the kidneys have been by previous infection, inflammation or vascular disease, the more dangerous does prerenal azotemia become for the individual. Since treatment for prerenal azotemia can be quite successful if begun early enough, it pays to act on the principle that all uremias are related basically.

Table 3

TYPES OF UREMIA

ORGANIC Renal Disease
- a) acute—oliguric, anuric
- b) chronic—polyuric, oliguric

FUNCTIONAL Renal Derangement
- a) Dehydration—water, electrolytes (hypo-osmotic, hyperosmotic)
- b) Hemodynamic—hemorrhage, shock, heart failure
- c) Hypercalcemia—bone disease, vitamin D, hormones
- d) Obstruction—post-renal
- e) Neurogenic (Trueta shunt)

In 1937 Harrison and Mason,[13] following Volhard, Fishberg and others, excluded prerenal azotemia and defined uremia as "only that symptom complex which occurs in conjunction with and as a result of the retention in the blood of urinary waste-products." In 1945, Bradley[14] defined uremia as that "clinical state associated with nitrogen retention and disturbances of body water due to renal insufficiency, regardless of etiology." This obviously includes the renal insufficiency initiated by prerenal disturbances and is, therefore, a satisfactory definition. The emphasis on the term "clinical state" in Bradley's definition is important because one should not jump to a diagnostic conclusion on any one laboratory finding. Uremia may be indicated whenever a patient has one or more of the following symptoms: anorexia, nausea, vomiting, diarrhea, weakness, pallor, apathy, itching, irritability, confusion, stupor, twitchings, hyperpnea, dehydration or edema.

The **management of uremia** follows more or less logically, more or less empirically, from the preceding discussion of pathogenesis and mechanism, provided the individual differences in etiology and types of physiological disturbances are taken into account, otherwise the treatment of uremia will become standardized, routine, thoughtless, and, on occasion, foolish or positively harmful. Thus, uremia following upon excessive vomiting and dehydration, will require the use of large quantities of parenteral fluid and the appropriate electrolytes. Most of the initially prerenal uremias fall in this category but with one major exception – the group originated by circulatory collapse. Here the immediate indication is not to pour in large amounts of diffusible fluid but to restore blood pressure, circulating blood volume and cardiac efficiency before irreversible renal and cerebral changes occur. The problem is relatively simple in massive hemorrhage in a person with a previously good heart. It is tantalizing in the case of acute myocardial infarction with prolonged circulatory collapse and oliguria. One must run the risk of cardiac failure and pulmonary edema in order to prevent prerenal uremia. Sufficient experience in this field for safe treatment is still lacking.

Ideally, **preventive** treatment of uremia based on anticipation of its occurrence is the best therapy (Table 4). This principle has been applied brilliantly to all conditions of the gastrointestinal tract associated with

vomiting, severe diarrhea or suction drainage of one type or another. Only accurate appraisal of the daily balance of fluid and electrolytes, and frequent blood chemical analyses, will furnish the proper guide to prophylactic treatment of prerenal uremia. Many lives have been saved by this simple bookkeeping.

Table 4

PREVENTION OF UREMIA

1. Observe; measure; consider; act.
2. Record and replace extrarenal loss.
3. Watch urine and serum electrolytes.
4. Maintain open urine-way.
5. Control use of renal-acting drugs.
6. Treatment of heart failure.
7. Fluid intake in chronic nephritis.
8. Diet in acute nephritis.
9. Parenteral fluid in hypercalcemia.
10. Use of BAL in Hg poisoning.

In severe acute nephritis, as well as in other oligurias, prevention of uremia consists of sharp restriction of salt and fluid intake and of protein, depending on carbohydrate and fat to furnish basal calories. Prompt recognition and treatment of early left ventricular failure are important in preventing circulatory renal impairment. The use of BAL early in mercury or arsenic poisoning may be of decisive prophylactic value. Checking of serum calcium values in patients under treatment with vitamin D, or large doses of testosterone for metastases from carcinoma of the breast, will indicate danger zones and suggest the need for vigorous measures to maintain renal function.

In patients with hypertensive disease or severe congestive heart failure, regardless of cause, over use of the low sodium regimen and of mercurials not infrequently leads to electrolyte depletion and serious metabolic disturbances ending in uremia. Serum electrolyte analyses during such diuretic treatment will save both the patient and the physician a great deal of distress and point to the type of restorative solution, preferably hypertonic.

In chronic renal disease with renal insufficiency at the pre-uremic level, the prevention of uremia consists in maintaining a large enough urine volume – at least 1500 to 2000 cc. – to offset accumulation of nitrogenous products, checking acidosis, and avoiding edema or excessive loss of salt. Careful appraisal of the patient's renal behavior in these various directions will individualize treatment. In general, a low protein diet – 30 to 50 Gm. – is indicated, with a relatively high caloric value to spare body protein. If there is edema, salt will be restricted; if there is a tendency to acidosis a few grams of sodium citrate or bicarbonate may be given daily. It should be remembered, as Addis and others have observed, that the kidney must do as much work to dilute the urine as to concentrate it in relation to the serum filtrate. Therefore, it pays to give enough salt to permit the kidney to

excrete urine with a specific gravity of 1.012 to 1.016. Patients with chronic renal disease are in danger of uremia should they develop anorexia and diminish their intake of fluid. The uncontrolled use of either acid-forming or alkaline compounds during renal failure is fraught with hazard for obvious reasons. Finally, uremia can be precipitated by the circulatory depression caused by excessive sedation.

During periods of necessary parenteral feeding, one must compromise with reality and not attempt to do the impossible either as to nutrition or as to maintenance of large urine volumes. One should rarely exceed 3 liters of fluid per day by the intravenous route in patients with uremia due to chronic renal disease. When serum sodium and chloride are both low, restoration is best carried out by infusing a solution of sodium chloride and sodium lactate or bicarbonate in the equimolar proportion of 3:1 or 2:1, to dilute the excess chloride in ordinary saline and furnish extra bicarbonate to correct present or potential acidosis. In the presence of hyperchloremia and low serum bicarbonate, the solution administered should be sodium bicarbonate or lactate in appropriate amount. Calcium may have to be given in some instances; potassium practically never in organic uremia and certainly never without chemical evidence of low serum values. Whatever solution is used, it must be borne in mind that renal function is inadequate to make the normal clear-cut selection between electrolytes; therefore, injection should be made slowly and frequent chemical analyses done to control the effects of the treatment. Careful records must be kept of intake and output, including gastrointestinal losses.

The question of parenteral injection of protein hydrolysates or plasma protein must be considered whenever oral intake of food is impractical for more than a few days. The amount of amino acids or, better, salt-poor serum albumin, need not be more than 20 to 25 Gm. of the former or 10 to 15 Gm. of the latter daily. Unpleasant reactions toward hydrolysates must be guarded against by slow infusion and trial of various brands until one is found for the particular patient.

When using antibiotics or other chemotherapy for infections, the dosage must be adjusted downward sharply to allow for severely impaired renal excretion of these compounds. This will prevent waste of more or less expensive drugs, and what is more important, may obviate the danger of serious sensitization or toxic reactions.

In uremia caused by acute toxic or other type of nephrosis, it is generally agreed that intake of fluids and electrolytes must be restricted to daily loss during the oliguric or anuric phase. However, once diuresis sets in, there is an imminent danger of electrolyte depletion because of poor tubular reabsorption. This situation resembles the salt-losing type of chronic nephritis and must be treated in the same manner by the oral or parenteral administration of mixtures, usually 2:1, of sodium chloride and sodium bicarbonate, (5 to 15 Gm. daily), with daily analyses of urinary sodium or chloride and frequent estimations of serum sodium, chloride and bicarbonate. It may be

necessary to follow this regimen for a few weeks. Any patient with severe renal insufficiency who is not edematous and is excreting large urine volumes is in danger of excessive electrolyte loss and should be carefully checked. In these days of widespread use of low sodium diets, it cannot be overemphasized that severe renal impairment is a contraindication to such a diet unless the physician can control his patient biochemically.

One of the most pressing questions in the treatment of uremia is whether one should resort to some type of irrigation or dialysis. This problem arises chiefly in the management of acute, reversible uremia but it also applies to some extent to chronic, irreversible uremia in the hope of tiding the patient over from a critical and premoribund to a little less precarious state. Snapper[15] and others have recently reviewed the indications for, and results of, the various procedures for the artificial dialysis of uremic patients and animals, and have arrived at the general conclusion that no one of these methods has been shown to improve the mortality statistics even in the supposedly reversible forms of uremia, as in lower nephron nephrosis. The reasons for these disappointing conclusions are the complexity of the procedure, the danger of peritonitis and ileus, the hemolytic reactions when blood is perfused through an apparatus, the difficulty in controlling hydration and electrolyte balance because of the type of solution used in the bathing fluid, or the diet taken by the patient or experimental animal. Yet there is still room for a simple, nontraumatic, nonhemolytic dialyzing machine and along with it a set of bedside chemical technics for the rapid clinical estimation of serum electrolytes, plasma volume and other essential data. With the present widespread interest in this field, rapid progress may be expected.

Summary

1. In view of the interrelationship of electrolyte and circulatory disturbances, the distinction between prerenal, or functional renal azotemia and true, or organic renal, uremia becomes superfluous even though differences in treatment and prognosis remain.

2. While the majority of the clinical manifestations of uremia are attributable to electrolyte and fluid imbalances, all potentially correctable, some specific toxemia related to protein catabolism may be an additional factor.

3. Principles of management of uremia are presented which accord with the pathogenetic mechanisms, in the hope that the individual patient's therapeutic cloth will be cut to fit the diagnostic and physiologic measurements of each case accurately, rather than by routine standards.

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COMPLICATIONS OF HIATUS HERNIA

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THE recognition of esophageal hiatus hernia as a pathologic entity is more widespread than might be anticipated. The impetus to diagnosis and clinical evaluation may be attributed primarily to the efforts of the roentgenologists. Careful study of the terminal esophagus and cardiac portion of the stomach is an integral part of every complete gastrointestinal study. For these reasons the incidence of hiatus hernia appears to be on the increase each year. Actually it is the incidence of recognition that is on the increase rather than the entity proper.

Hiatus hernia may be an incapacitating condition but is rarely a fatal one. The most troublesome complications of hiatus hernia are from bleeding, occult or massive. Peptic ulcers may occur and produce the disabling symptoms seen in ulcers elsewhere. Apparently perforation of an ulcer in a

Fig. 1. Large para-esophageal hiatus hernia in 60 year old white man treated on numerous occasions for severe secondary anemia now believed due to occult bleeding from herniated stomach. Anemia totally corrected following transthoracic repair of hiatus hernia.

Fig. 2. Para-esophageal hiatus hernia in 63 year old white woman presenting typical peptic ulcer symptoms. Well-defined gastric ulcer apparent in the hiatus hernia. Complete relief of all symptoms followed transthoracic repair.

hiatus hernia is a rare entity as is strangulation of the incarcerated portion of the stomach.

In patients with esophageal hiatus hernia the stomach usually protrudes from the celomic cavity into the posterior mediastinum. This extension of the retroperitoneal portion of the stomach through the hiatus classifies this entity as a sliding hernia. A sac is also present since the reflection of the peritoneum on the anterior wall of the stomach is drawn through the hiatus by the herniated viscus. The recognition of this type of herniation is important in its surgical repair. Whereas inguinal sliding hernias descend externally into the scrotum, the hiatus hernia enters the posterior mediastinum and there causes compression or displacement of adjacent viscera. When one considers that the space normally occupied by the terminal third of the esophagus may be forced to accommodate one-half the volume of the stomach and its contents, it becomes apparent that anatomic compensation must occur. Usually the increased bulk of the hernia is taken up by the left pleural space; the resultant compression of the left lung is probably of no significance. Occasionally, however, there will be noticeable deviation of the cardiac silhouette to the right and pronounced displacement of the thoracic aorta to the left. It is in this latter case that the patient may complain of anginal type pain, exertional dyspnea and intermittent back or

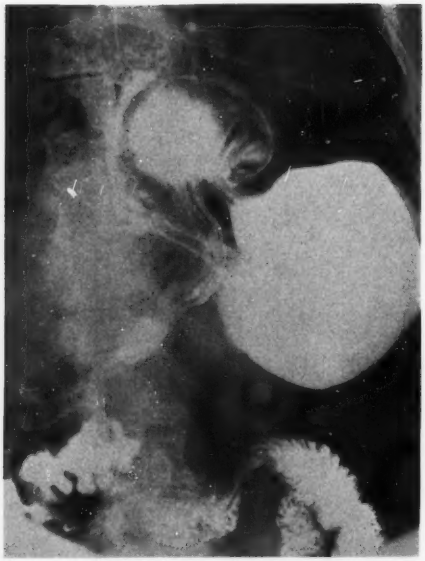

Fig. 3. Unusual manifestation of hiatus hernia. There is volvulus of stomach, and antrum of stomach appears herniated through the esophageal hiatus. Patient complained primarily of postprandial distress, fullness and frequent vomiting after meals.

shoulder pain. It is not the herniated viscus producing the symptoms in such a case but rather the displaced adjacent structures.

Any hernia that is unreduced is subject to complication; the hiatus hernia is no exception. Whereas the various inguinal herniations contain an assortment of viscera, the hiatus hernia consists almost exclusively of stomach and omental fat. For this reason the symptoms and resultant complications are usually associated with disturbed gastric physiology. The expected complications of hiatus hernia may be classified into three groups: 1. Hemorrhage, 2. Ulcer, 3. Volvulus. Each of these groups may be subdivided by the various manifestations and each may be an integral part of the other.

1. Hemorrhage
   a. Occult
   b. Massive — (Hematemesis, (Melena
2. Ulcer
   a. Peptic
   b. Traumatic
3. Volvulus

Hemorrhage: By far the most important complication of hiatus hernia is bleeding (fig. 1). This may be manifested only by a hypochromic anemia

without symptoms to localize the source. According to Brick,[1] the incidence of hiatus hernia among 3448 patients undergoing upper gastrointestinal roentgen examination was 8.93 per cent. This significant figure must be kept in mind when investigating any case of anemia which may be attributed to occult bleeding from the gastrointestinal tract.

The exact mechanism of bleeding in hiatus hernia is not understood. Undoubtedly many will bleed from ulceration of the gastric mucosa; on the other hand, all peptic ulcers in hiatus hernia do not manifest a bleeding tendency. Harrington[2] has suggested that bleeding is more frequently associated with incarceration of the hernia and erosion of the included gastric mucosa. The fact remains, however, that bleeding may vary quantitatively from occult to massive hemorrhage.

Ulcer: Many of the symptoms attributed to hiatus hernia parallel those of peptic ulcer.[3,4] Nevertheless, few of these cases can be proven to have a demonstrable ulcer within the incarcerated hernia (fig. 2). This is surprising when one postulates the physiologic disturbance produced by an incarcerated portion of stomach whose filling and emptying processes are obviously abnormal. However, it must be kept in mind that failure of roentgenographic demonstration does not mean that an ulcer has not been or is not

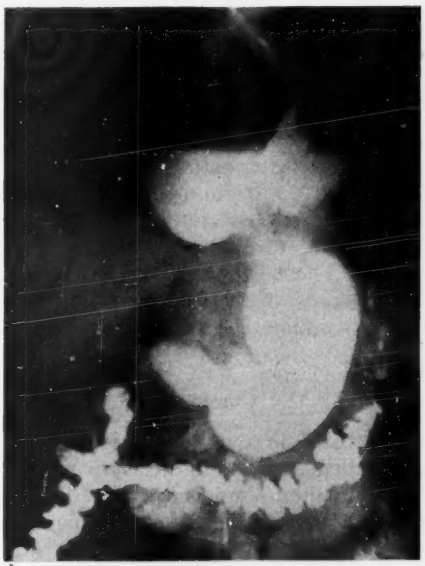

Fig. 4. Large esophageal hiatus hernia. Esophagus displaced anteriorly, still well-outlined by the contrast medium. Herniated portion of stomach partially incarcerated and incompletely obstructed. Patient complained of regurgitation following each meal and nocturnal retrosternal pain. Symptoms completely removed by transthoracic repair of hernia.

present. It must also be remembered that most patients with persistent severe symptoms of hiatus hernia have developed an "ulcer regime" of their own through dietary trial and error. It is reasonable to assume that many ulcers and mucosal erosions in hiatus hernia are transient in character since the size and contours of the sac may be in a constant state of flux.

The so-called "traumatic" or "callous" ulcers are described in many texts.[5] These ulcers are said to be produced by the trauma of the adjacent, compressing structures on the impinging gastric mucosa. Such lesions may differ from the true peptic ulcer if they are produced mechanically; however, this matter is subject to question. In all probability the ulcer found in a hiatus hernia is no different than any other peptic ulcer.

Volvulus: The stomach is an extremely flexible viscus with four major attachments. The cardia and the pylorus constitute the most inflexible points of fixation, the ligaments of the greater and the lesser curvatures the more flexible (fig. 3). As the hollow viscus is forced into the mediastinum, a definite distortion of its normal contours takes place. The stomach may undergo torsion or fold back on itself so that the pylorus may be drawn above the cardia. Radiographic studies may demonstrate a bizarre configuration of the stomach with numerous fluid levels. In such cases, it becomes apparent that the organ is no longer capable of normal physiology. In this state the stomach is chronically obstructed to some degree.

Volvulus of the stomach may produce distressing clinical symptoms that are associated with obstruction and incarceration[2] (fig. 4). These patients vomit frequently soon after meals. Often regurgitation and eructation are forced by the patient for relief of severe retrosternal distress. Symptoms in these cases are usually worse after eating and when reclining. Often there will be severe pain behind the sternum that may simulate angina. When the viscus becomes distended by gas and fluid, there may be severe dyspnea and anxiety on the part of the patient who describes his discomfort as "pressure on my heart." These patients frequently impose voluntary social exile upon themselves because of the constant urge to regurgitate and eructate. In addition, they consume large quantities of various remedies with questionable value.

Comment

Other diseases are listed in the literature as complications of hiatus hernia. Authors have called attention to the association of gastric carcinoma, esophageal ulcer, diverticulum, esophagitis, hypertrophic gastritis, varices, etc. [1,3] with hiatus hernia. Actually these are separate entities and there is little evidence that they are conditions caused by the hernia.

Hiatus hernia may produce serious complications. Too frequently the impression has been given in the literature that this is a benign lesion capable only of mild dyspepsia and eructation. There is increasing clinical evidence which shows that some hiatus hernias are incapacitating by these

ulcer symptoms alone. The most serious complication, however, is the massive hemorrhage which may occur. Hiatus hernia must always be suspected when there is unexplained bleeding from the gastrointestinal system.

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NEEDLE BIOPSY OF THE LIVER

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Introduction

NEEDLE puncture of the liver was first performed by Stanley[1] in 1833 to drain an abscess, and was first employed as a diagnostic procedure by Lucatello[2] in 1895. A few investigators in Europe have given accounts of diagnostic liver biopsies prior to 1939, but this technic did not come into widespread use until the report of Iversen and Roholm[3] in 1939 on liver biopsy in 160 cases. With the advent of the war and increased incidence of hepatitis, general use gradually was made of liver biopsy as a diagnostic technic. Needle biopsy was utilized during the war chiefly as a means of studying the pathology of infectious hepatitis. Since then it has proved valuable in other conditions as well.

The first method of liver biopsy consisted of simple aspiration of a few liver cells with a smear made of the material obtained. Iversen and Roholm used a similar aspiration technic, but removed a plug of tissue which proved to be more satisfactory. A number of investigators have taken a specimen for biopsy at operation [4,5] or have used small incisions to obtain one. Biopsy specimens also have been obtained during peritoneoscopic examination.[6] A refinement of the early technic has been the "Vim" Silverman needle used to secure a plug of tissue satisfactory for pathologic study.

Investigators have used the intercostal approach, the subxyphoid, and the subcostal. Many have been concerned over possible tears in the liver capsule that might be caused by respiratory movement with the intercostal approach. Others, fearing possible perforation of other viscera with the subxyphoid approach in the patient who does not have a palpable liver, have limited the use of this technic to patients with palpable livers. Ricketts[7] has used the intercostal approach in some 300 cases, and Schiff[8] in 700 cases; both feel that this is the method of choice and both have had no complications using this method. Hoffbauer[9] has used the subcostal approach in patients with palpable livers, and biopsy under peritoneoscopic visual control in patients without hepatomegaly.

For any diagnostic procedure to be worth-while, there must be a minimum of resultant mortality. Prior to the Iversen and Roholm report there were 6 deaths in 403 cases. Iversen and Roholm reported 160 cases in 1939 without a single death. Other investigators have also reported large series without any mortality. Among others, Gilman and Gilman[10] had no deaths in 906 biopsies, Van Beek[11] had no deaths in 200 biopsies, Hatieganu[12] none in 45, Hoffbauer[9] none in 65, Davis et al[13] none in 79, Schiff[8] none in 700.

Dickinson[14] none in 119, Webb and Werthammer [15] none in 70. Sherlock[16] records 2 deaths in 264 biopsies, Volwiler, and Jones[17] 1 in 234 biopsies, Dible et al[18] 1 in 126 biopsies. These figures indicate that with the necessary precautions, diagnostic needle biopsy of the liver is a relatively safe procedure.

Liver biopsy has been of great value in furthering our understanding of infectious (epidemic) hepatitis and serum hepatitis. The contributions of Iversen and Roholm,[3] Sherlock,[16] Dibble, McMichael and Sherlock[18] have been outstanding and have clarified the pathology of infectious hepatitis which had not been well understood previously. It also has been helpful in our knowledge of other liver conditions such as cirrhosis, brucellosis,[19] and phosphorus poisoning.[20] Liver biopsy has been used in estimating the prognosis in patients with cirrhosis, and in evaluating the therapeutic program for cirrhosis. [17,21] Liver biopsy has been used to evaluate and correlate liver function tests with pathologic alterations [5,22,23] and has indicated further the use and limitations of liver function tests. As indicated by Volwiler and Jones,[17] liver function tests merely show impaired liver function and are not a measure of exact diagnosis. Liver function tests do not disclose whether the impaired function is due to cirrhosis, metastatic malignancy, primary hepatoma, or other pathologic conditions. The multiplicity of functions of the liver, and the vast number of tests employed indicate that an exact diagnosis of liver disease is frequently difficult on the basis of liver function tests alone. Frequently it is much simpler and more satisfactory to do a liver biopsy than to run a gamut of liver function tests that do not give an exact diagnosis. Some conditions such as primary and metastatic cancer, hemochromatosis, amyloid disease, and Gaucher's disease may

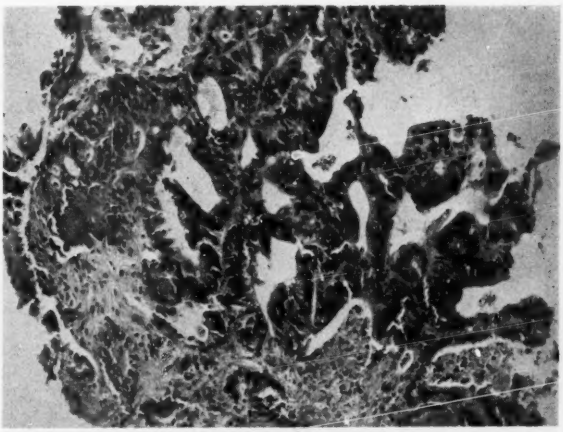

Fig. 1. Adenocarcinoma, metastatic in liver, obtained by needle biopsy. Primary site unknown (x-70).

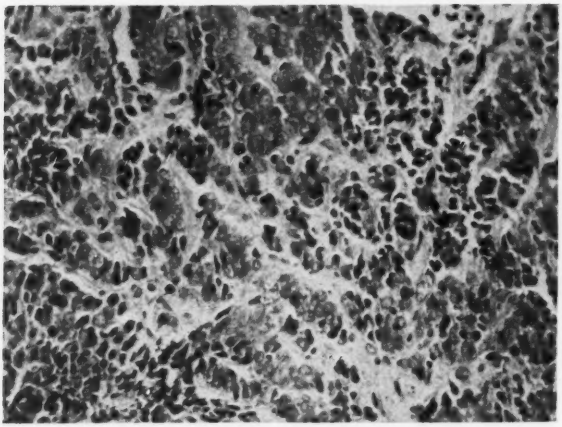

Fig. 2. Metastatic carcinoma, probably bronchogenic (x-200).

be diagnosed ante mortem only by liver biopsy or an exploratory laparotomy.

Many of the difficulties that have complicated needle biopsy of the liver have arisen because of the moribund condition of the patient or because certain precautions were not followed. The exact technic and method used appears not to have made much difference in the published mortality figures, whether the subcostal, subxyphoid, or intercostal approach was used. The contraindications to needle biopsy of the liver are: 1. presence

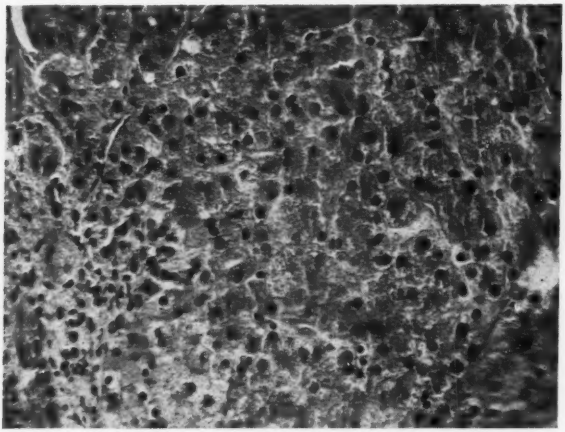

Fig. 3. Hemochromatosis of liver (x-200).

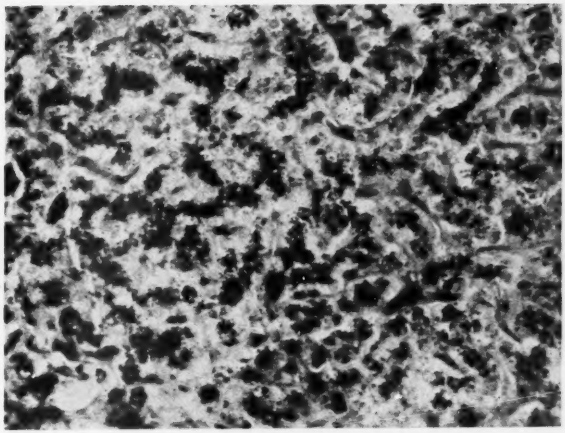

Fig. 4. Hemochromatosis of liver with "Berlin Blue" stain[24] to show hemosiderin deposits (x-200).

of pyogenic infection in the liver; 2. increased bleeding tendency; 3. increased prothrombin time.

The approach to liver biopsy at the Cleveland Clinic has been entirely similar to that reported by Hoffbauer.[9] Biopsy has not been attempted in cases of pyogenic infection, in patients with a bleeding tendency, or unless the prothrombin time was at least 75 per cent. The "Vim" Silverman needle has been used with a subcostal approach in patients with palpable livers. When a large nodule was present in the liver, an attempt was made to obtain a specimen from the nodule. In the patient who did not have palpable liver, biopsy was obtained with the "Vim" Silverman needle under peritoneoscopic visual control. We have been hesitant in using the intercostal approach because of possible tears in the liver capsule. We have also been reluctant to use the subxyphoid approach in the absence of a palpable liver because of the possible perforation of other viscera. The actual technic of the "Vim" Silverman needle has been adequately described by others.

Results

TABLE 1

ADEQUACY OF BIOPSY

	Silverman Needle	With Peritoneoscopy	Total
Satisfactory specimen	46	21	67
Unsatisfactory specimen	4	4	8
			75

The results obtained in 75 liver biopsies are recorded in Table 1. A specimen adequate for pathologic diagnosis was obtained in 67 out of 75 biopsies. Fifty of the biopsies were done in patients with hepatomegaly, using the subcostal approach. Twenty-five biopsies were obtained in patients without an enlarged liver by use of the "Vim" Silverman needle under peritoneoscopic control.

TABLE 2

DIAGNOSES FROM LIVER BIOPSY

Diagnosis	Number of Patients
Cirrhosis	26
Metastatic malignancy	18
Fatty metamorphosis	9
Primary liver cell carcinoma	3
Bile stasis	3
Hemosiderosis	3
Malignant melanoma	2
Hemochromatosis	2
Hepatitis	2
Amebic abscess	1
Gaucher's disease	1
Biliary cirrhosis	1

The diagnoses established by liver biopsy are presented in Table 2. Although the most common condition found by biopsy was cirrhosis, only a small number of patients with cirrhosis were subjected to liver biopsy. However, biopsy may be of value in some patients with moderately advanced cirrhosis, who show little change in liver function. In addition, the presence of impaired liver function may be due to causes other than cirrhosis which may be discovered by biopsy. Liver biopsy also may help in the diagnosis of cirrhosis and in evaluating the prognosis and therapeutic program the patient has been following.

Nine patients were found to have fatty metamorphosis of the liver, a condition that is considered precirrhotic, and a condition that is usually amenable to treatment.

Eighteen patients were found to have metastatic cancer. A positive diagnosis in these cases seems of value from a prognostic point of view. Liver biopsy is practicable and may save the patient the expense and discomfort of a needless laparotomy. In addition there are many patients in whom there is evidence of metastatic malignancy, but in whom the primary site remains obscure. Liver biopsy may be the simplest diagnostic procedure in these cases, and may yield the most information.

It must be stressed that a negative biopsy is worthless in suspected cancer. The metastatic nodule may easily be missed by the biopsy needle. We have made every attempt to biopsy a nodule when present. A repeat biopsy when

the first one is negative and when there is a strong suspicion of metastatic malignancy is clearly indicated.

Primary liver cell carcinoma was found in 3 cases. The first biopsy in one of these cases showed only cirrhosis; a second biopsy showed a primary hepatoma to be the cause of the patients tremendous hepatomegaly.

Bile stasis, strongly suggestive of an obstructive biliary tract lesion such as neoplasm of the pancreas, was found in 3 patients. Volwiler and Jones[17] and Webb and Werthammer[15] have stressed the value of liver biopsy in the diagnosis of jaundice.

Metastatic malignant melanoma was diagnosed ante mortem in 2 cases, hemochromatosis in 2 cases, and Gaucher's disease in 1 case. It is unlikely that a positive diagnosis could have been established ante mortem without a liver biopsy unless the more hazardous procedure – exploratory laparotomy – was done.

Hepatitis was found in only 2 cases. This is not an index of the frequency of hepatitis, but an indication that the newer liver function tests are usually accurate in diagnosing this condition. Liver biopsy was seldom necessary to establish the diagnosis.

Various complications of needle biopsy of the liver have been reported. The relative safety of the present procedure, following the precautions already cited, has been discussed. The most frequent complication of liver biopsy has been bleeding following the biopsy. Other writers have reported finding duodenal[13] and colonic mucosa in the biopsy specimen. The patients in whom this occurred, however, survived the procedure. Using the precautions and technic already mentioned, we have had no deaths in the 75 biopsies performed. There has been no appreciable bleeding in these patients, and none required transfusions. Biopsy in 3 patients yielded clear bile, but no difficulty ensued. The patients suffered little if any discomfort following the simple needle biopsy. A few patients had some discomfort for several hours after the procedure with pain in the right upper quadrant, referred to the right shoulder; however none had fever, leukocytosis, or other complications. Somewhat more discomfort was experienced for 24 hours after the peritoneoscopic examinations.

Liver biopsy by the Silverman needle is preferable to exploratory laparotomy with a small incision as advocated by some[4] as biopsy entails less risk of morbidity and death.

Establishing a diagnosis in the cases cited was important and would not have been possible without a liver biopsy or an exploratory laparotomy.

Case Reports

Case 1. Metastatic Adenocarcinoma. A 50 year old man came to the Cleveland Clinic with a history of anorexia and gradual loss of 26 pounds in the past 4 months. He had been constipated for 3 months and had had a dull pain in the right flank for 1 month. Physical examination revealed a large nodular mass in the right upper quadrant, presumably in the liver. This mass was biopsied with a Silverman needle and a pathologic diagnosis of adenocarcinoma was made (fig. 1).

This case illustrates the point that frequently a liver biopsy will elicit more information concerning the patient than any other method of study with the exception of exploratory laparotomy.

Case 2. Metastatic Carcinoma. A 47 year old man complained of severe abdominal pain for 2 weeks, mild dyspnea for 2 years, severe dyspnea for 2 months, cough productive of blood streaked sputum for 2 months, and clotted blood in vomitus on one occasion. He had lost 28 pounds in weight. Physical examination revealed an enlarged lymph node above the right clavicle, fleeting fine rales in the chest, and a tender liver descending 7 cm. below the costal margin. Laboratory tests were noncontributory. Roentgenograms of the chest showed an irregular nodular mass involving chiefly the anterior mediastinum. Liver biopsy with the Silverman needle showed undifferentiated carcinoma (fig. 2).

The primary site of carcinoma in this patient was not evident, and might have required considerable searching to determine, although it probably was bronchogenic.

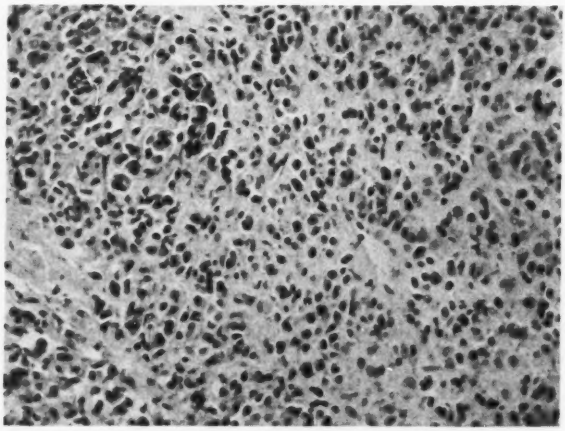

Fig. 5. Melanosarcoma of liver (x-200).

Extensive studies, and possibly even thoracotomy, might have been necessary to have established the diagnosis of metastatic malignancy if liver biopsy had not revealed the disease.

Case 3. Hemochromatosis. A 40 year old woman complained of pain in the right flank, backache, and excessive thirst for approximately 6 months. There was a past history of excessive wine consumption. During the examination, the patient had a sudden onset of generalized weakness, headache, nausea and vomiting. Positive findings on physical examination were: Kussmaul breathing, acetone odor of the breath, dehydration, dark gray color of the skin, and severe hepatomegaly. The liver descended 11 cm. from the costal margin in the right midclavicular line. Blood sugar was 588 mg. per 100 ml. and CO_2 combining power was 14.4 volumes per cent. Prothrombin time, and bromsulfalein liver function tests were normal. She was treated in a routine manner for her diabetic acidosis. Liver biopsy with the Silverman needle revealed many refractile brownish pigment granules which reacted positively to iron stains in both liver cells and connective tissue. She subsequently died, and severe hemochromatosis of liver, spleen and pancreas was found (figs. 3 and 4).

Hemochromatosis is often suspected before death, but usually a positive diagnosis of this condition is not ascertained. Liver biopsy readily disclosed the nature of this patient's diabetes and hepatomegaly.

Case 4. Malignant Melanoma. A 41 year old man complained of frequent nausea, gaseous dyspepsia, and distention for 8 months. He had had an enucleation of his left eye 5 years previously. The surgeon was contacted and reported that the eye had been removed because of separation of the retina and atrophy of the globe, and that there had been no evidence of malignancy in the pathologic specimen. On examination, the left lobe of the liver descended 6 cm. below the costal margin, and the right lobe 9 cm. below the costal margin. One definite nodule was palpated. Roentgenogram of the chest, intravenous urogram, and barium enema examination were essentially negative. Routine blood count and laboratory studies were normal. Liver function tests (prothrombin time, bromsulfalein, and albumin/globulin ratio) were normal. Liver biopsy with the Silverman needle was done over the nodule palpated. The pathologic specimen showed round and polyhedral epithelial cells occurring in solid groups. The nuclei were prominent and many cells contained brownish nonrefractile pigment. An iron stain showed no bluing of the pigment granules. The pathologic diagnosis was malignant melanoma (fig. 5).

In view of the negative history of malignancy in the enucleated eye, a positive diagnosis of malignant melanoma could not have been made without liver biopsy.

Case 5. Primary Hepatoma. A 71 year old Chinese man complained of right upper quadrant pain, anorexia, weakness and swelling of the ankles for approximately 2 months. His diet was questionably deficient and there had been some excess alcoholic intake. Positive physical findings included the presence of a large firm smooth liver that extended below the iliac crest. Roentgenographic examinations were all negative except for indications of an enlarged liver shadow. Complete laboratory examinations were also negative except for severe impairment of liver function. The prothrombin concentration was 72 per cent of normal. There was 45 per cent bromsulfalein retention in 30 minutes, using 5 mg. of dye per kg. body weight. Cephalin cholesterol was 2 plus, and thymol turbidity was 8 units. There was a reversal of the albumin-globulin ratio, the albumin 2.7 Gm. per 100 ml. and the globulin 5.4 Gm. per 100 ml. A needle biopsy was done which showed only moderate cirrhosis. Because of the definite enlargement of the liver and the strong suspicion of a primary hepatoma, a second liver biopsy specimen was obtained. The latter showed neoplasm formed by atypical epithelial cells which were growing as single cells without attempt at duct formation. The cells were of moderate size and there were many mitotic figures. The pathologic specimen was thought to be compatible with a primary liver cell hepatoma.

The true nature of the patient's disease could not have been diagnosed by the liver function tests alone, since they indicated impaired liver function but did not disclose the underlying malignancy. The diagnosis could have been accomplished only by postmortem examination, exploratory laparotomy which was contraindicated in view of his liver function, or by simple needle biopsy of the liver. This case illustrates the point that a needle biopsy of the liver may miss a neoplastic lesion. The first biopsy was negative for carcinoma; only after the second biopsy was the neoplasm found. If there is a strong suspicion of carcinoma, a second liver biopsy should be done even though the first is nondiagnostic.

Summary

"Vim" Silverman needle biopsies of the liver have been done in 75 patients at the Clinic. They were not performed on patients with evidence of: 1. pyogenic infection, 2. increased bleeding tendency or 3. increased prothrombin time. Biopsy with the Silverman needle alone was done on 50

patients with hepatomegaly, and biopsy with the needle under peritoneoscopic control in 25 patients without an enlarged liver. Satisfactory specimens were obtained in 67 of the 75 cases. The only complications of the biopsies were the aspiration of bile in 3 cases; none manifested postbiopsy bleeding, fever, or leukocytosis.

Needle biopsy using the necessary precautions is a safe diagnostic procedure and was helpful in 26 cirrhotic cases in which liver function tests and the clinical picture failed to give an accurate diagnosis. It also confirmed the diagnosis in 18 patients with metastatic malignancy. The simple procedure of liver biopsy saved many of these patients the expense and discomfort of an exploratory operation.

Biopsy was indicated in the diagnosis of obstructive jaundice in 3 cases. Primary liver cell carcinoma, a condition in which a positive diagnosis is seldom made ante mortem, was discovered in 3 patients. Other conditions in which liver biopsy was of paramount importance in arriving at a diagnosis were malignant melanoma, hemochromatosis, and Gaucher's disease.

Liver biopsy with the "Vim" Silverman needle has proved to be an important procedure in the diagnosis of obscure liver disease.

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SENILE SPASTIC LID DEFORMITIES—THEIR SURGICAL CORRECTION

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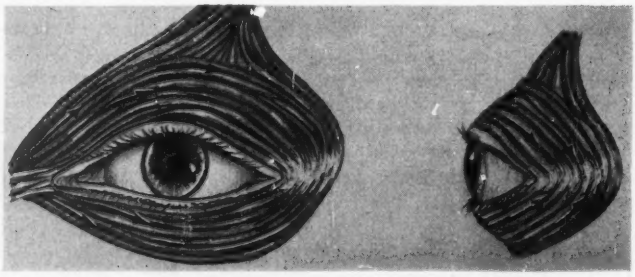
SENILE lid deformities usually involve the lower lid and result from spastic disorders. The correction of either entropion or ectropion must be aimed toward obtaining proper physiologic position of the lid border in order to avoid epiphora, trichiasis or deformity of the orbital fissure. The ideal operation is one which would produce permanent results so that the aged patient would not be subjected to subsequent operative procedures which entail added risks for the elderly patient.

If the underlying cause is understood, a surgical means for correction is more easily chosen. The musculature of the lids and the tarsal plate are the bases of the deformity and must be used to correct the malposition. By examining the muscle fibers of the lid, it can be observed that the orbicularis muscle describes arcs having curvatures in two different directions.[1] One direction is the semi-encirclement of the palpebral fissure with the arc being directed downward in the lower lid and upward in the upper lid (fig. 1a). The second direction is an arc with its concavity toward the orbit formed by the muscles being molded to the shape of the eyeball (fig. 1b). These muscles have their attachments from the lateral and medial raphe; from this area comes their main support on contracture. The muscles pass over a tarsal plate which contributes to the maintenance of the lid's form.[2] With aging there is a loss of orbital fat, a loss of skin tone, and as a result when the muscles of the orbicularis contract they tend to form a cord rather than an arc. As a result the tarsal plate is forced to bend inward or outward as



(a) (b)

Fig. 1. (a) Curvature of muscles in upward and downward arc. (b) Curvature of muscles in anterior-posterior arc.

Fig. 2. (a) Preoperative ectropion right lower lid. (b) Postoperative result.

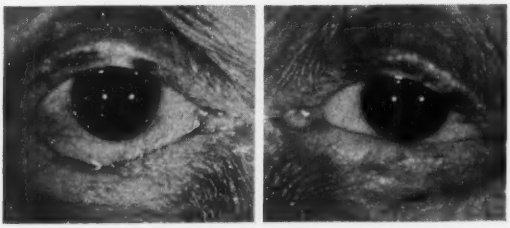
one of its borders receive insufficient support, which results in ectropion as shown in Figure 2a or entropion as shown in Figure 3a.

To correct this faulty position and fulfill our requirement the operation of Kuhnt-Szymanowski is the most permanent and satisfactory [3,4,5] for senile entropion. The Figure 2a shows a patient with ectropion before operation. The lower lid is everted, the conjunctiva red, thickened and spotted with a seondary infection. The patient suffers from epiphora and repeated attacks of acute conjunctivitis.

The operation of Kuhnt-Szymanowski is started at the intra-marginal line, the gray line, that runs the length of the lid. A knife blade inserted here splits the lid into leaves. The anterior consists of the skin, fibers of the orbicularis muscle and lash border; the posterior consists of the tarsal plate and conjunctiva. The incision should be carried to the outer canthus, starting slightly medial to the midline of the lid at A, (fig. 4a). The incision must not pass to the skin surface or through the tarsal plate to the conjunctiva, and care must be taken not to injure the roots of the lashes.

The second step is removal of a section of tarsal plate in order to shorten the plates' length so that it will regain its form to support the reconstructed lid; at the same time redundant conjunctiva can be removed. This is done by removing a triangular section of the inner leaf of the lid (fig. 4a), the base

of which should range from 5 to 10 mm. This must be of sufficient size to place the leaf of tarsus and conjunctiva snugly against the eyeball. Black silk number 4 sutures are then passed through the edges of the wound and then through the tarsal plate and conjunctiva. They must not pass too near the wound edge as they may pull out of the fragile tissues. They must neatly approximate the edges of the wound. The suture first tied is that at the apex of the wound and then progressively the sutures are tied toward the base. This should result in a snug fitting of the conjunctiva against the eyeball. Kuhnt contributed this part of the operation.[6] Szymanowski described the correction of the outer leaf of the lid.[7] The latter method consists of extending the splitting of the lid out into the skin at the outer canthus from D to B (fig. 4a), a distance slightly greater than the length of the base of the tarsal triangle which was removed. This part of the incision should slant up and outward. A second incision DC should begin at the outer canthus and extend down and outward and end at C directly below B. The distance



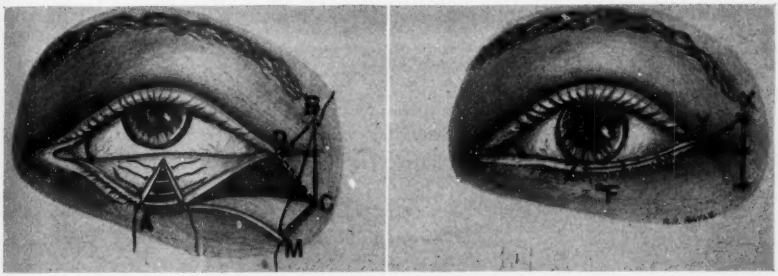
(a) (b)

Fig. 3. (a) Preoperative entropion right lower lid. (b) Postoperative result.

DC should be about two times as great as DB. A third incision should form CB and the outlined triangle of skin, DBC, be removed. The anterior leaf of the lid is then undermined so that its outer corner, M will reach B. The portion of lid margin that now lies beyond the outer canthus must have its edge bearing the cilia removed. Sutures of black silk number 4 are passed through the apex of the free lid border at M, and deeply through the muscle and skin at B so that the area denuded of skin is covered by the excess skin flap that formerly lay over the lid. Sutures are then placed at intervals, as in Figure 4b, to give a satisfactorily smooth union of the skin surface. I have modified the placing of sutures to include from 3 to 4 black silk number 6 sutures along the lid border uniting the tarsal leaf and skin leaf of the wound at their free border. Formerly only one suture was used at F that did not include the lid border, but passed through the two leaves and tied over the skin surface. I feel that by this means one can be more sure of the control of the outer leaf, having the hair follicles pointing outward, and prevent gapping of the wound. If the sutures in the lid border are not tied tightly but just firmly enough to control the free edges, and if fine sutures are used, no indentation of the lid border results and no complica-

tion of trichiasis arises. Suture X is placed first and then, starting with suture Z, the sutures are progressively arranged toward X. In this way the amount of skin covering the lid border can be controlled easily and any excessive skin can be removed between Y and X. After the operation is completed the shortened lower lid lies against the eyeball and its outer end is slightly elevated.

Firm dressings are used over the wound to prevent an accumulation of body fluids therein and to immobilize the lid. The sutures may be removed in from 4 to 7 days as the progress of healing indicates. The results of such an operation are illustrated in Figure 2b which shows the postoperative results of Figure 2a approximately 1 year after surgery. Lytton's[8] recently introduced subcutaneous splitting of the skin of the lid seems an unnecessary measure, and a study of this procedure indicates that some of the basic advantages of the Kuhnt-Syzmanowski operation may be lost.



(a) (b)

Fig. 4. (a) Kuhnt-Szymanowski operation showing lid split in two leaves; composite stages. (b) Kuhnt-Szymanowski operation showing closure of wound.

The correction of spastic entropion is best controlled by the technic of Wheeler. I have previously reported 7 cases[9] and 2 more have been added to the series, one of which is used here to illustrate the procedure. The patient (fig. 3a) suffered constantly from epiphora, recurrent conjunctivitis, and had a history of superficial keratitis. These symptoms resulted for the most part from the mechanical irritation of the eyelashes against the eyeball and cornea.

The Wheeler operation is performed with a primary skin incision 6 mm. below the normal lid margin. This incision should include only the skin structures. The incision starts nasally to the center of the midline of the lid and, following a course parallel to the lid edge, is carried out to 1 cm. beyond the orbital margin into the zygomatic region (fig. 5). This method is used to enter under the skin and dissect the skin from the underlying orbicularis muscle and in this way exposes the muscle in an area extending from the incision up to the lash border and from the incision about 6 to 10 mm. downward.

A strip of muscle 4 to 5 mm. wide is then dissected from the orbicularis muscle starting at the innermost edge of the skin incision and extending to an area directly below the outer canthus. This strip of muscle must lie immediately over the lower border of the tarsal plate. The muscle dissection sweeps out and upward following the natural arc of the muscle fibers. The dissected strip of muscle is then freed at its outer edge, A (fig. 5).

The muscle is then stretched, brought upward and outward and attached to the periosteum slightly superior to and lateral to the orbital tubercle. The muscle strip in position must pass up and firmly over the lower border of the tarsal plate.

Two chromic number 3 sutures are mattress-stitched through the muscle strip and passed firmly into the periosteum, B (fig. 5). The overlying skin is then closed with interrupted black silk number 4 sutures and a tight dressing applied. The skin sutures can be removed from the fourth to seventh day, again depending on the postoperative reaction of the area and healing of the skin.

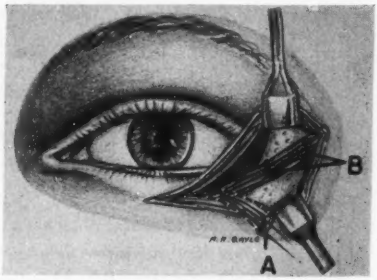


Fig. 5. Composite stages of Wheeler orbicularis muscle transplant operation.

The placement of the muscle fibers gives new pressure to the lower edge of the tarsal plate and restores a more nearly normal muscle arc. The under skin scarring of the operative site gives a firm skin area over the lower eyelid.

The postoperative result of such a case can be observed by comparing Figure 3a with Figure 3b.

Summary

Appropriate surgery for senile spastic lid deformities should be more frequently employed. I believe that the Kuhnt-Szymanowski technic modified with the placement of lash border suture for ectropion and the Wheeler procedure for entropion provide:

1. Physiologic lid border position
2. Good support for the lid
3. No disfigurement of the palpebral fissure
4. Low incidence of recurrence.

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CYSTINURIA AND CYSTINE CALCULI

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CYSTINURIA, or the presence of abnormally large and consistent amounts of cystine in the urine, is a result of permanent physiologic upset of protein and sulfur metabolism. Cystine is a sulfur-containing amino acid present in protein foods which, in normal metabolism is oxidized principally to sulfate with a smaller amount converted to taurine. In the patient with cystinuria, however, there is failure of intermediary enzyme oxidation of cystine into sulfate and cystine is excreted in the urine in amounts which may be as high as 1 Gm. per liter of urine in a 24 hour period. Normal urine contains only a few mg. (0.8-80 mg. daily) cystine per liter.

This incurable metabolic defect has been recognized for nearly 100 years, but has escaped widespread attention of the medical profession because of the rarity of cystine lithiasis and hence of clinical manifestations. Many patients pass through life without knowledge of their metabolic abnormality. It has been estimated by Eppinger[1] that approximately 2.7 per cent of those with cystinuria develop calculi and subsequent clinical symptoms. An indication of the relative incidence of cystinuria can be gleaned from the findings of Lewis[2] who reported 29 positive cystine urine tests in 11,000 healthy young men and women.

Cystine lithiasis is a rapidly progressive variety of urinary calculosis with a high tendency to recurrence. A few patients, unaccountably, are prone to form calculi in the urinary tract while the majority escape this complication. Experimental clinical and pathologic studies suggest that some lesion of the tubular epithelium of the kidneys initiates calculosis with cystine deposition on a damaged renal tubular epithelium. This occurs in a manner similar to the calculus formation in phosphaturia, oxaluria, and hyperparathyroidism.

The biochemistry of cystine metabolism is confusing, but salient investigations indicate that the amount of cystine excreted by a cystinuric patient is proportional to protein intake. Cystinuria cannot be eliminated completely as small amounts will continue to be excreted even in a state of starvation. The oral administration of cystine does not increase the excretion of cystine which oxidizes to sulfate, as would cystine recovered from the urine if fed to a cystinuric patient. However, methionine and cystine feedings do augment cystine excretion and most experimental studies indicate that cystine in the urine is probably derived from sulfur containing proteins and not from exogenous injection of cystine itself.

An increase in cystine content of urine has been observed[3] in specimens

stored from 12 to 24 hours, due, presumably, to gradual decomposition of an unstable cystine complex which liberates free cystine.

Familial Occurrence

Cystinuria has a definite hereditary tendency which has been established by numerous investigators. Inasmuch as this tendency is transmitted as a mendelian recessive, it is unusual for all members of a family to show cystinuria. Of those who do show positive cystine urine tests only a few form stones: however; potentiality exists in all people with elevated cystine excretion. Cases 1 and 2 of our series exhibit this familial tendency.

Age Incidence

Men seem to be affected more frequently than women (a ratio of 65 to 27)[4] with no predilection for any particular age group. Cystine calculosis has been described in an infant of 2 months and in a man of 80 years. Most cases are recognized in younger persons only when the first attack of renal colic appears. All of our patients had their first clinical manifestations during childhood or adolescence.

Diagnosis of Cystinuria

Cystinuria can be established by either of two simple laboratory procedures. The first consists of examining the concentrated urinary sediment of a cystinuric suspect. The characteristic flat, colorless hexagonal cystine crystals (fig. 1) in the urinary sediment are diagnostic of cystinuria. If the urine is alkaline at the time the specimen is collected, further crystal formation may be observed after acidifying the urine and allowing it to stand several hours before re-examining the concentrated sediment.

The diagnosis may be confirmed accurately and easily by the use of the qualitative cyanide-nitroprusside test of Brand, Harris and Biloon.[5] A modification of this test is used at the Cleveland Clinic. Most standard texts on clinical laboratory methods or biochemistry include this test or a variation[6].

Clinical Manifestations

The clinical manifestations of cystine lithiasis are similar to those produced by stones of other chemical composition. Recurrent periodic renal or ureteral colic was present in all of our patients having either multiple or single stones. Two of 6 developed unilateral staghorn calculi, a type of renal stone reported both as frequent[7] and unusual.[8] As demonstrated in the 6 case histories, the most serious feature in cystinuria is the almost inevitable recurrence of cystine lithiasis. The patients are disturbed by periodic colic, the passing of stones, and re-formation of calculi after removal.

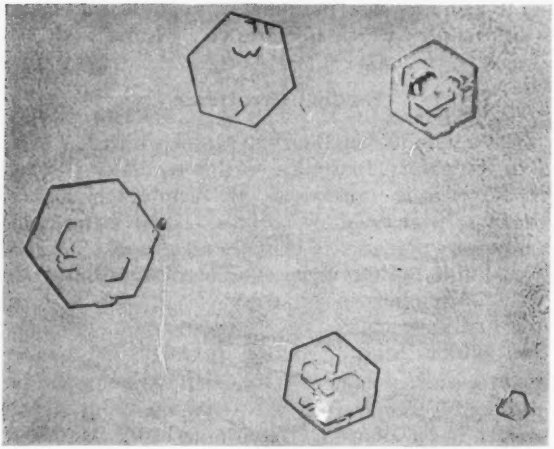

Fig. 1. Characteristic hexagonal cystine crystals present in urinary sediment.

Roentgenologic Observations

Roentgen examination of the genitourinary tract will show localization of cystine stones if they contain inorganic substances. Pure cystine appears nonopaque,[8] and cystine capsules given orally cannot be visualized. If a stone does not cast a shadow in preliminary films of the abdomen, then stones of cystine, uric acid, or xanthine composition should be suspected.

Cystine Lithiasis

Cystine lithiasis usually is unilateral and often recurs at the same site. Cystine stones comprise approximately 2 to 4 per cent of all renal calculi. Prien and Frondel[9] found 3.8 per cent cystine in a series of about 700 calculi. Cystine stones usually are found in acid urine and characteristically are oval, smooth, polished, chalky white or light yellow in color, with a soapy appearance. They can be cut like hard yellow soap and may become yellow-green with exposure to air. Microscopically they are composed of multiple hexagonal (fig. 1) crystals within an organic framework colored by yellow pigment.

Cawker[7] believes hemisection of the stone and examination of the nucleus, as well as the outer layer of the stone, may indicate the initiating factor.

Case Reports

Case 1. A youth of 18 came to the Cleveland Clinic with a complaint of intermittent attacks of colicky right flank pain which lasted from 1 to 3 days. One year previously he first experienced severe sharp costovertebral pain radiating around the right flank into the groin and upper right thigh. The pain was accompanied by nausea and vomiting which gradually subsided after hypodermic injections.

He had incurred a second attack 6 months later and subsequent routine urinalysis demonstrated persistent pyuria. An intravenous urogram performed several days before admittance to the Clinic indicated impaired function of the right kidney. There was no history of hematuria or passing of stones.

Physical examination disclosed a well developed, well nourished youth in no apparent distress. No costosvertebral tenderness or palpable abdominal masses were evident. Urinalysis disclosed 4 plus albuminuria and 10 to 15 white cells and occasional red blood cells. The blood urea was normal.

A repeat urogram failed to show any right kidney function. A cystoscopy and bilateral retrograde pyelograms demonstrated considerable right hydronephrosis with apparent ureteropelvic obstruction. No opaque calculi were identified. Operation disclosed no ureteropelvic obstruction. The right upper ureter was dilated and when it was followed downwards a sizeable stone was palpated approximately 10 cm. below the ureteropelvic junction obstructing the ureter. A ureterolithotomy was performed and a 10 by 7 by 2 mm. calculus removed which, on laboratory analysis, proved to be composed of cystine.

The postoperative course was uneventful and the patient subsequently was placed on an alkaline ash diet and potassium citrate. The residual dilatation of the right kidney pelvis gradually disappeared and the patient remained asymptomatic. Urine pH has been consistently maintained at 7.5 or higher by the urinary alkalinization regime.

Case 2. A youth, aged 18, brother of the patient in case 1 was admitted to the Cleveland Clinic Hospital with severe left costovertebral pain of 2 hours' duration. During the previous 6 months he had suffered from recurrent bouts of severe left flank pain which generally began in the left costovertebral angle. Gross hematuria usually followed the onset of the attacks.

Fig. 2. Arrows indicate multiple filling defects in left kidney pelvis produced by cystine stones, Case 2.

The patient was in acute pain and a generalized abdominal tenderness existed, most pronounced in the left upper quadrant and left costovertebral angle. A flat film of the abdomen and intravenous urogram demonstrated multiple faint shadows in the lower pole of the left kidney and in the region of the left renal pelvis (fig. 2). Two additional shadows in the course of the lower left ureter suggested calculi. The right kidney and ureter were apparently normal.

A contralateral stellate block completely relieved the pain for approximately 2 hours, a method of amelioration as effective as that usually obtained with morphine and atropine. At cystoscopy a catheter passed up the left ureter met resistance near the kidney pelvis, and it was believed ureteral stones had been dislocated by the passage of the catheter. A subsequent pyelogram indicated early hydronephrosis and multiple filling defects in the pelvis and inferior calyx of the left kidney. No shadows were seen in the ureter at this time in contrast to the previous roentgen examination. Urinalysis for cystine was strongly positive.

The patient was placed on a urinary alkalinization program with the administration of 2 Gm. of sodium bicarbonate and potassium citrate 4 times a day; in addition, a moderately low cystine and methionine diet replaced his regular diet.

During the following 8 months the urine pH was maintained at 8.0 or above and the patient passed 13 cystine stones (fig. 3) with occasional brief bouts of renal colic. Serial flat films demonstrated a diminishing number of left renal calculi with no evidence of the formation of new stones.

Case 3. A white youth, aged 16, came to the Clinic complaining of pain on micturition and passing stones in the urine. A review of his history revealed that he had passed stones in the urine at the age of 2 but had remained asymptomatic until the age of 7 when he developed severe left flank and back pain. A subsequent left nephrectomy was performed for nephrolithiasis; no disease was demonstrated in the right kidney. This youth had experienced 2 attacks of dysuria and gross hematuria during the 3 weeks previous to his first examination, and on one occasion had passed a small stone. Physical examination was essentially negative. Cystine crystals were prevalent in the urine and the cystine test was strongly positive. Initial roentgenogram of the abdomen and intravenous urogram revealed calcification in the course of the lower right ureter, manipulation of which resulted in the removal of two small stones which had been lodged in the midportion. Analysis identified these calculi as cystine stones. The patient was instructed on hospital discharge to maintain an alkaline ash diet and to drink an abundance of water.

During the following 2 years the patient had no recurrence of symptoms and discarded his dietary regime. A few months after returning to an unlimited diet the right costovertebral pain and soreness returned. Roentgen examination at that time demonstrated 3 small calcifications in the course of the right ureter. Inasmuch as no ureteral obstruction was present and kidney function was satisfactory, no operative procedure was considered. The patient was advised once again to follow a low purine alkaline ash diet, maintain a high fluid intake, and alkalinize the urine by the use of potassium citrate 2 Gm. 4 times a day.

Case 4. A boy, 2½ years of age, was first brought to the Clinic in 1927 having experienced intermittent poorly defined abdominal pain for several months. Roentgen examination disclosed several large calcifications in the bladder region and intravenous urogram confirmed the suspicion of bladder calculi. A suprapubic cystolithotomy was performed and 2 large calculi removed. Two years later a large stone in the left kidney pelvis was removed shortly after its appearance and in 1934 additional new calculi were removed from the right kidney. In 1938 2 calculi, cystine in composition, were removed from the bladder. The patient was then placed on an alkaline ash diet with no recurrence of lithiasis for 5 years.

In 1943 another calculus in the left kidney gradually became smaller on resuming a strict dietary regime. During the following years the patient was unable to follow his diet and developed consequently a staghorn calculus (fig. 4) in the left kidney pelvis with

resultant nonfunction of the left kidney and persistent pyuria. Despite the presence of an urea splitting infection, the stone in the left kidney gradually diminished in size and the urinary infection was controlled with difficulty with prolonged use of sulfanilamides, penicillin, and streptomycin. The patient has been asymptomatic during the past 2 years and the urine is consistently positive for cystine. Urine alkalinization has been maintained between pH 7.5 and 8.0 on an alkaline ash diet supplemented at times with alkalinizing drugs.

Case 5. A married woman, aged 30, was admitted to the Clinic Hospital with severe right flank colic. At the age of 6 she was known to have passed a small stone at micturition and 2 years later a stone was removed from the left renal pelvis. At the age of 21 she had a left nephrectomy for recurrent calculus and nonfunctioning left kidney.

A flat film and intravenous urogram demonstrated an opaque stone in the inferior calyx of the remaining right kidney. The renal colic quickly subsided with symptomatic treatment and since no residual kidney damage was evident the patient was discharged. She returned in 3 weeks with the stone displaced into the kidney pelvis and recurrent renal colic. This calculus was removed surgically and the patient had an uneventful convalescence. The patient's family history revealed that an uncle had bilateral renal calculi, and a nephew renal lithiasis. She was placed immediately on urinary alkinalization and an alkaline ash diet.

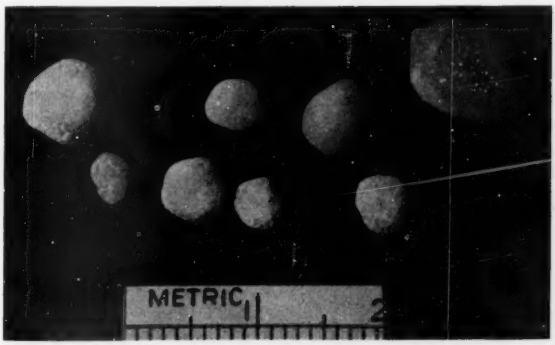

Fig. 3. Smooth cystine stones, Case 2.

The patient remained well for approximately 2 years when she developed recurrent right flank colic. A retrograde pyelogram disclosed a small stone in the lower right ureter with slight right hydronephrosis and hydroureter. This and several other small stones passed easily after a right ureteral meatotomy. The patient returned to an alkaline ash diet and for the past 18 months has been free of urinary complaints.

Case 6. A young man, aged 19, was admitted to the Clinic in 1923 complaining of recurrent bouts of left flank pain. Intravenous urogram and flat film of the abdomen revealed a calculus in the right kidney pelvis. A right pelviolithotomy and nephrostomy were performed and a large calculus was removed.

The patient returned to the Clinic in 1926 with recurrent right kidney calculus and a small stone in the left ureter. After left ureteral dilatation the small stone was passed without difficulty. During the next 5 years the right kidney stone became a staghorn calculus filling the pelvis and calices. When he returned to the Clinic a colon bacilli infection was present which could not be controlled medically. A right nephrectomy was performed for calculus pyonephrosis but a stone analysis was not reported.

During the next 15 years the patient passed occasional gravel in the urine but had no

severe pain or colic. In 1946 he experienced severe left lower quadrant pain with radiation into the left groin. Shortly thereafter he passed a stone the size of a pin head from the lower left ureter. After left ureteral dilatation several small stones passed and a renal calculus was removed by pelviolithotomy; a nephrostomy tube was used for drainage for approximately 1 month. Stone analysis was positive for cystine and consequently the patient was placed on an alkaline ash diet and urinary alkalinization. Repeated roentgen examinations of the genito-urinary tract during the last few years have not demonstrated new calculi. The patient has felt well and has been able to follow the outlined diet without difficulty.

Treatment

Surgery of cystine lithiasis, such as ureterotomy, pelviolithotomy, and cystotomy, is similar to that used in the treatment of any other type of stone. In the absence of surgical indications the treatment should be directed toward prevention of recurrent stone formation. Klemperer and Jacobi[10] were first, in 1914, to advise alkalinization of the urine with 6 to 10 Gm. sodium bicarbonate daily. Subsequently it has been learned that the alkaline urine resulting from this medication merely keeps cystine in solution and does not effect the underlying metabolic disturbance. Crowell[11] first demonstrated disintegration of cystine stones by alkalinization of the urine and repeated alkaline lavage of renal pelves in a case with bilateral renal cystine calculi. Adequate fluid intake is recommended for all patients with this disease, as for any patient with stones, in order to maintain sufficient urinary output to keep the urinary constituents in complete solution.

Fig. 4. Staghorn calculus in left kidney pelvis, Case 4.

Alkalinization of the urine can be maintained best by the administration of sodium bicarbonate or potassium citrate in 1 or 2 Gm. doses 4 times a day. As a check on efficiency of alkalinization, the patient should be taught to test the urine by the use of indicator paper such as methyl red or nitrazine in an attempt to maintain a urine pH of 7.0 or higher. Any concomitant urinary disease should be corrected and special attention directed toward the prevention of any form of urinary tract obstruction.

An alkaline ash diet low in sulfur protein is valuable in maintaining alkaline urine as well as in diminishing the concentration of cystine urinary output per unit volume. Some patients can be treated successfully on the diet without recurrence of stones.

Case 4 is an example in which the patient's inability to follow the prescribed alkaline diet may have precipitated the formation of recurrent calculi. Previously on a strict dietary and alkinalization regime, a staghorn renal calculus had decreased in size as indicated by roentgen examination. Serial urograms in case 2 demonstrated an apparent decrease in size of pelvic stones. The patient passed numerous stones (fig. 3) without apparent ureteral obstruction while on urinary alkalinization. There is no evidence that new calculi have been formed subsequently.

None of the 6 patients in this group have shown ill effects from long urinary alkalinization. When a patient was maintained on a strict alkaline ash diet and adequate urinary alkalinization, the formation of new cystine calculi was absorbed and a high urine pH (7.5+) sustained. Progress roentgen examinations demonstrated objective evidence of diminishing stone size.

Periodic ureteral dilatation and renal pelvis lavage with weak alkali calculi after operative removal; repeated instrumentation is often undesirsolutions have been used successfully[11] to increase stone dissolution. We have preferred to rely upon adequate alkalinization to prevent recurrent able.

Summary

Cystinuria is a rare, incurable metabolic defect in which abnormally large amounts of cystine are excreted in the urine. Diagnosis is established by the discovery of characteristic flat hexagonal crystals in the urinary sediment or by a positive cystine urine test.

Clinical attention usually is prompted by symptoms of urinary calculi. This variety of urinary calculosis has a high tendency to recurrence. A program of urinary alkalinization and an alkaline ash diet low in sulfur proteins has been effective in reducing the incidence of stone recurrence in the 6 cases studied.

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PIGMENTED TUMORS OF THE CENTRAL NERVOUS SYSTEM

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PIGMENTED tumors of the central nervous system include the pigmented meningioma, primary leptomeningeal melanoma, and secondary malignant melanoma. Although the last group is commonly recognized, the first two are not so well known. In 1940, Ray and Foot[1] reported two instances of primary melanotic tumors of the meninges resembling meningiomas. One case in this category will be presented. While there has been some controversy over the existence of primary leptomeningeal melanoma, several well-documented cases have been described [2,3,4,5] and now appear in some texts.[6] One instance will be described briefly, although it has already been reported in detail by Netherton.[7] Secondary malignant melanoma of the central nervous system makes up the third group; this is by far the most common of the pigmented tumors and similar series have been reported by other authors. [8,9,10,11,12,13] No attempt to debate the various theories of origin for the melanoma will be made, as this aspect of the problem has been extensively dealt with previously.[14,15,16,17]

Pigmented Meningioma

Schnitker and Ayer[11] in 1938 described a case which they stated resembled an "atypical meningioma from examination of the surgical specimen alone", but which they designated malignant melanoma. Ray and Foot[1] reported a tumor of the spinal cord and a posterior fossa neoplasm, with surgical removals and 5 and 2 year survivals respectively at the time. Both tumors were said to resemble pigmented meningiomas and Foot[18] later classified these two atypical growths as such. In the present case, the postoperative course and survival were characteristic of a benign neoplasm and the histologic configuration was in all ways compatible. So far as can be determined from a review of the literature, this represents the third reported instance of pigmented meningioma. The importance of recognition of this group of pigmented tumors is obvious.

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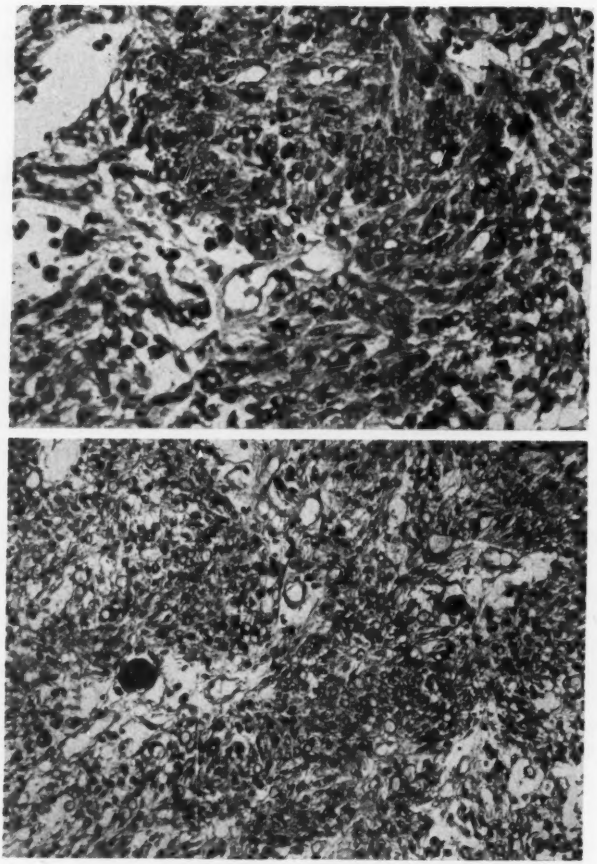
(a)



(b)

Fig. 1. (a) Pigmented meningioma, showing intracytoplasmic pigment in the meningothelial cells. (b) Psammoma bodies in the pigmented meningioma.

Case Report

A white laborer, aged 45, entered the Cleveland Clinic complaining of low back pain and left sciatica. Two years previously he first noted pain down the left lower extremity and numbness along the outer aspect of the left lower leg and foot. The leg pain followed an injury to the back after having lifted a 100 pound sack of potatoes; at the time he felt something snap in his back. The leg pain was aggravated by coughing and sneezing. Shortly thereafter the patient developed numbness of the right foot, and some pain behind the right knee when he coughed or sneezed. The strength of the left lower extremity was impaired. There were no sphincter disturbances except for a short period of urinary retention following a novocain injection (caudal block?) given elsewhere for the relief of

pain. The weakness of the left leg had progressed so that he required crutches when walking.

The general physical examination was essentially normal. Blood pressure 150/90. There was a draining sinus above the thyroid gland which had been present since the opening of a cyst some time previously. Neurologic examination was normal except for the back and lower extremities. There was severe weakness and and wasting of the left thigh, calf, and foot, absence of the left patellar reflex and of both Achilles reflexes. There were paresthesias radiating into both feet, and hyperesthesia of the anterolateral aspects of the left lower leg and foot. The pain in the leg was not intensified by compression of the jugular veins. Routine laboratory studies were entirely normal. The spinal fluid examination showed no cells, a trace of globulin, and 30 mg. per cent of protein. Lumbosacral x-rays were interpreted as normal.

The patient was admitted to the hospital and lumbar myelograms showed obstruction of the dye medium at the level of the joint space between the second and third lumbar vertebrae. With a working diagnosis of either protruded intervertebral disk, or spinal cord tumor such as neurofibroma, lumbar laminectomy was carried out. No extradural mass

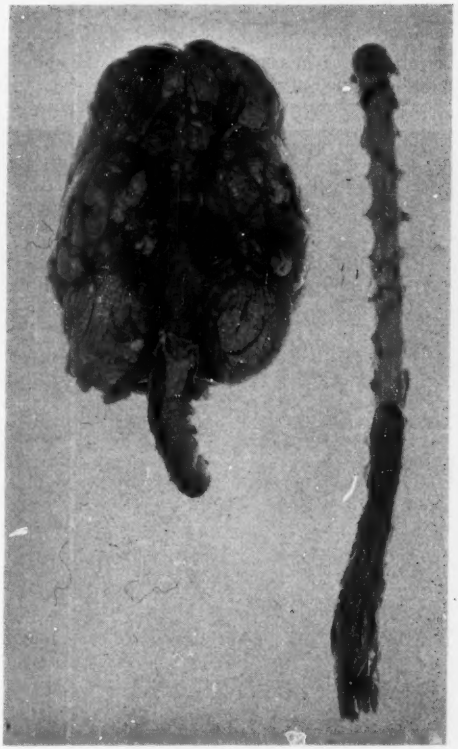


Fig. 2. Primary leptomeningeal melanoma, showing the diffuse leptomeningeal pigmentation of the brain, the subdural mantle of melanoma about the lower cord and cauda equina.

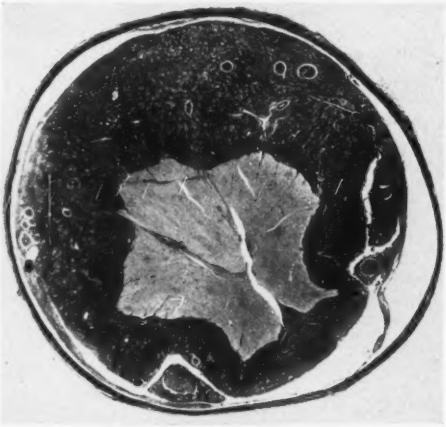


Fig. 3. Primary leptomeningeal melanoma. Cross section of the spinal cord, showing the annular subdural disposition of the melanoma.

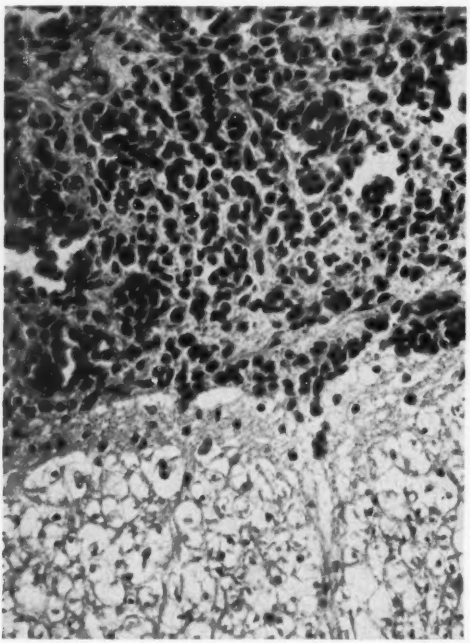


Fig. 4. Nevus-like cells densely infiltrating leptomeninges and sharply demarcated from the cord substance.

was found. The dura was opened to disclose a large, slate blue, rubbery tumor mass, filling the spinal canal from L-2 to L-4. The tumor appeared to be well-encapsulated, and about 5 cm. in length. To effect removal, the right third lumbar root was divided between silver clips, the tumor capsule was incised, the interior evacuated, and the capsule excised along with a circular area of dura. The tumor appeared to extend through the intervertebral foramen on the right, and to lie partly paravertebrally. Because frozen section study was reported as melanoma, the operation was abandoned at this point.

The postoperative convalescence was uneventful. There was a definite foot-drop on the left, and an orthopedic appliance was prescribed. When last heard from, 8 years after the operation, the patient's wife reported that he had gained 53 pounds over his previous best weight, and that his general condition was excellent. He had not completely regained the use of the left lower extremity but was free from pain.

In May 1947, 6 years after operation, one of us (J. B. H.) reviewed the microscopic sections to make a diagnosis of pigmented meningioma.

Pathology

The gross specimen consisted of multiple small portions of velvety, blackish-brown material, portions of which were covered by a tannish-brown fibrous capsule.

Microscopically the neoplasm was formed by cells of meningothelial type, polyhedral and spindle-shaped, 10 to 12 microns in width and up to approximately 40 microns in length, arranged as compact dark staining sheets with irregular pale staining zones (fig. 1a). The cell cytoplasm was moderately abundant, for the most part dark staining in the compact zones, and often containing fine granules or irregular, small clumps of brown, nonrefractile pigment. The cell nuclei were round or oval, well differentiated, generally without prominent nucleoli, and frequently pale or vesicular as if containing a large clear vacuole. No mitoses were apparent. The pigment retained its brown appearance after stains for iron. The vessels were rather evenly dispersed and of simple character. Scattered, small, round psamomma bodies were present (fig. 1b). There was a slight tendency to whorl formation. Architecturally, the neoplasm most typically resembled the type I, variant 4 meningioma of Cushing and Eisenhardt.[19]

Discussion

Differentiation between the pigmented meningioma and tumors of the melanoma group is relatively easy due to the rather typical meningothelial appearance of the cells, the uniform and sheet-like arrangement of the tumor, and the lack of nuclear dedifferentiation. Except for the presence of the intracellular pigment, the neoplasm is characteristically meningioma.

Primary Leptomeningeal Melanoma

Cases of primary leptomeningeal melanoma have been described by Ford,[6] Akelaitis,[20] Shapiro and Kellert,[4] Da Costa and Love,[21] Wilcox,[22] Winkelman, Gotten and Silverstein,[17] Farnell and Globus,[2] and Kessler.[3] The following case has been reported previously.[7]

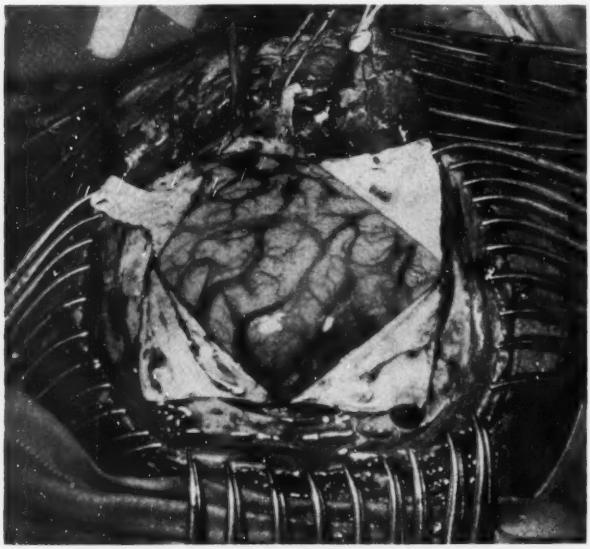


Fig. 5. Case 1. Secondary malignant melanoma. Gross appearance of cortical melanotic lesion at time of left parietal craniotomy.

A 17 year old white man reported to the Clinic complaining of blurring of vision, headache, poor memory, vomiting and occasional numbness of the right hand, all of 7 weeks' duration. Bilateral papilledema with xanthochromic spinal fluid under 700 mm. water pressure was found. He had a hairy mole which had been present since birth covering about one-third of the body surface. Observation of pneumoencephalograms indicated an obstructive hydrocephalus. Suboccipital craniotomy and cerebellar exploration were carried out (W. J. G.) and a bluish-gray mantle was found covering the posterior surface of the medulla, suggesting an angioma. One month later, cervical laminectomy revealed extension of the previously noted bluish-gray, subdural, extramedullary mass. Two weeks later the patient died and an autopsy was performed.

Pathology

The autopsy findings were briefly as follows:

Over the lower part of the face and the upper part of the chest, both anteriorly and posteriorly, there was a large, diffusely distributed and darkly pigmented nevus. There were many smaller, similar pigmented areas scattered over the body, varying in size from 1.0 to 5.0 cm. in diameter, and covered by an abundance of coarse, black hair. The brain weighed 1565 Gm. The dura was essentially normal. The pia arachnoid over the base of the brain was slightly thickened, opaque, and of brown appearance (fig. 2). From the optic chiasm back to the pons and medulla, the pia arachnoid was thickened and brown. The dura of the spinal cord was normal. On opening this a mantle of grayish-brown tissue was disclosed, apparently occupying the

site of the pia arachnoid, completely surrounding the cord from the level of the medulla to the cauda equina and varying in thickness from 1.0 to 5.0 mm. The greatest thickness was from the midcervical to the lumbar region. The dura stripped without difficulty from this tumor mantle and was not infiltrated at any point. The spinal nerves were surrounded by tumor tissue as they emerged from the cord, but otherwise were distinct from it. The cord was of fairly normal outline, and its anatomic markings were not unusual. There was no apparent reduction in the size of the spinal cord so far as the upper cervical region was concerned; the lower cervical region, however, presented some distortion of the cord with an irregularity of its shape (fig. 3) a diminution in the size, and some loss of the normal anatomic markings. Grossly, however, there was little or no infiltration by tumor.

Microscopic examination of sections from the cerebral cortex, olfactory bulb, thalamus, pons, medulla, and cerebellum showed small, round, or polyhedral cells occurring in groups or diffusely distributed in the leptomeninges. In some areas these cells were numerous, producing severe thicken-

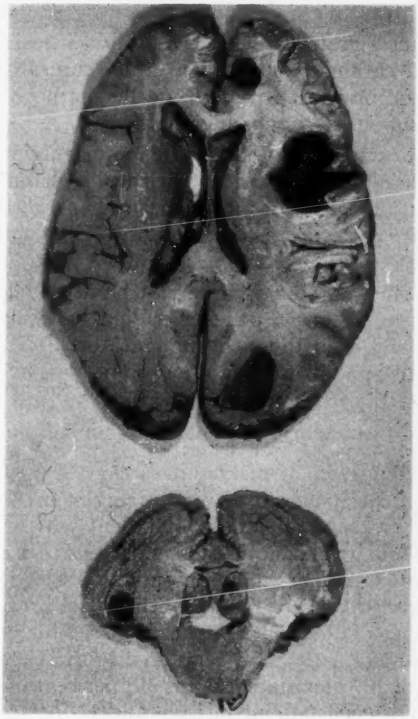


Fig. 6. Case 2. Secondary malignant melanoma, nodular metastases in brain.

ing of the leptomeninges and extending along pial vessels into the brain tissue but usually well delimited from this. The cells possessed little cytoplasm and the nuclei were of irregular configuration, dark staining and without prominent nucleoli or mitoses. The cells were separated in part by an increased connective tissue of the leptomeninges and in the connective tissue were occasional cells of chromatophore type laden with fine, brownish, nonrefractile pigment granules which gave a negative reaction for iron. Sections through the spinal cord presented similar but more intense infiltration of the leptomeninges by the nevus-like cells described above. These surrounded nerves but did not penetrate them, and the sheath of cells was generally well demarcated from the spinal cord substance (fig. 4).

The leptomeninges were sharply delimited from the subdural space and in no instance was the dura infiltrated. The cells forming the mantle about the spinal cord revealed variations in size and staining property and rarely there were mitoses. However, nuclear dedifferentiation was never severe. The anatomic diagnoses were: primary leptomeningeal melanoma, diffuse, of brain and spinal cord; pigmented nevus, diffuse, of face and chest; pigmented hairy nevi, multiple.

It is thought that a growth, such as was found in this case, arises from the leptomeningeal chromatophores. The usual clinical picture is that of increased intracranial pressure, stiff neck, sterile xanthochromic spinal fluid and mental clouding, i.e. a "tumor meningitis."

The cells almost exclusively infiltrate the leptomeninges with little or no penetration of brain or cord substance. Nuclear dedifferentiation is not that which is found in true malignant melanoma. In general, there is no indication of growth activity except for a rare mitosis. The aggressiveness of true malignant melanoma is not evident in any area.

A primary leptomeningeal origin cannot be accepted as such unless a careful search fails to disclose a primary malignant lesion in the eye, skin or visceral organs and even then, the presence of intracerebral melanotic nodules would challenge an interpretation of primary origin.

Secondary Malignant Melanoma

Grant[12] reported 7 cases of melanotic sarcoma from the neurosurgical service of Peter Bent Brigham Hospital occurring from 1914 to 1926. There were 49 metastatic intracranial lesions in the 13 year series, making a 14 per cent incidence for the melanotic tumors. In 1932, Dunlap[13] reported on 95 metastatic tumors of the brain, citing only 2 cases of melanoma (2.1 per cent incidence). In 1939, Courville and Schillinger[9] reviewed 18 cases of metastatic melanoma of their own. Fourteen were included from a series of 1060 cases of intracranial tumors registered in the Cajal Laboratory and as part of a group of 107 metastatic tumors (12 per cent incidence for melanomas in the group of metastatic neoplasms, and 1.3 per cent of intracranial tumors in general). In 1940, Moersch, Love, and Kernohan[10] found 34 cases

(in 19 of which the diagnosis was verified by operation or necropsy) of metastatic involvement of the central nervous system in a general group of 500 melanomas seen from 1930 to 1939. Of those melanomas showing local recurrence or metastases, 10 per cent involved the central nervous system.

Fourteen cases of secondary malignant melanomas of the central nervous system were encountered at the Clinic in a group of 85 metastatic tumors occurring in 1294 intracranial neoplasms. Of these the following 3 cases are presented.

Case Reports

Case 1. A 40 year old white man was admitted to the hospital because of a progressive right spastic hemiplegia, aphasia, headache and mental changes of one month's duration. Air studies showed a ventricular shift to the right. A left parietal craniotomy disclosed a coal black melanoma in the cortex (fig. 5). Following surgery, the patient's wife gave the further history of the removal of an enlarging dark mole from the skin and the appearance 4 months previously of a pigmented spot on the nose. Death occurred on the second postoperative day. No autopsy was performed.

Case 2. A 64 year old white woman was seen at the Clinic with a 3 months' history of progressive mental deterioration, left lower facial weakness, dysphagia, and generalized weakness. She was arteriosclerotic, and this was thought to have etiologic implications until 4 days later when the patient became stuporous and lumbar puncture revealed xanthochromic fluid under increased pressure. By this time she had developed a left hemiparesis and left Jacksonian convulsions. A right parietal craniotomy disclosed a large right subcortical hematoma which was evacuated. She died with hyperthermia in 2 days. An autopsy revealed multiple cerebral (fig. 6) and extensive visceral metastatic lesions with extension of tumor about vessels adjoining neoplasm. The primary site could not be determined.

Fig. 7. Case 3. Secondary malignant melanoma. Vitiligo and patchy depigmentation of the hair of the chest and the eyelashes. Onset of vitiligo coincided with the development of central nervous system symptoms from metastatic melanoma.

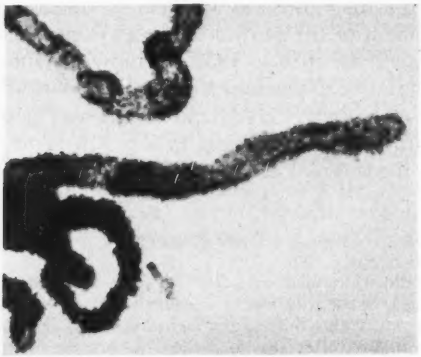


Fig. 8. Case 1. Secondary melanoma from brain. Teased preparation showing sheath-like formations about vessels.

Case 3. A 29 year old white man entered the hospital complaining of headache, left Jacksonian seizures, and progressive weakness of the left extremities of 3 months' duration. The examination showed a left hemiparesis with increased intracranial pressure. It was noted that the patient had vitiligo and depigmentation of the eyelashes and hair over the chest (fig. 7). There were no nevi in the skin lesions. This skin difficulty was coincident with the onset of headaches 3 months previously. The electroencephalogram showed right cerebral localization. The patient became less responsive, and a right frontal craniotomy was performed. A reddish brown, vascular subpial tumor was enucleated along with a recent subcortical clot. Pathologic examination revealed malignant melanoma showing extensive necrosis and zones of hemorrhage. After surgery the family gave the information that 18 months before his examination here a pigmented nevus was surgically excised from the back, and a diagnosis of melanotic sarcoma had been made. The patient was still living 3 months following surgery.

Discussion

In this present series the metastatic lesions to the brain occurred as multiple, circumscribed, though not encapsulated, nodular areas (figs. 5 and 6) of variable size and in most instances of brown or black coloration, but occasionally presenting a gray or white appearance. The tissue on section was soft, friable and often characterized by severe hemorrhage, both within the tumor and in the adjoining brain tissue, at times sufficient to grossly obscure the underlying neoplasm. Microscopically the tumor was typical of malignant melanomas found in other locations. The cells were rounded, polyhedral, or spindly-shaped, and varied in size from 10 or 12 microns to large cells 25 or 30 microns in diameter. The nuclei presented dedifferentiation, evidenced by the presence of prominent nucleoli, vesicularity of the nuclei, and mitoses which often were of atypical character. The cells were arranged in either broad sheets or in groups, the latter being most evident in the regions in which the connective tissue coverings of the brain were infiltrated. In one instance tumor cells were practically obscured by the presence of dense masses of brown, nonrefractile intracellular pigment. In

other instances there was a moderate to intense fine granular pigmentation of the individual cells and of chromatophores in connective tissue adjoining the tumor. Rarely the pigment was sparse, occurring in relatively few cells, broad areas of the tumor showed no pigmentation. Stains for iron were negative except in an occasional focus of old hemorrhage.

The brain tissue adjoining the tumor was infiltrated by solid tumor masses and did not show a diffuse single cell infiltration. A prominent feature in some cases was tumor extension along the vessels of adjoining brain tissue, the neoplastic cells forming a thin sheath encasing the vessel (figs. 8 and 9).

The clinical diagnosis of secondary malignant melanoma of the central nervous system is not easy, although it can be made more frequently if the possibility is kept in mind. A history indicating the presence of a malignant or suspiciously malignant mole or a tumor of the choroid is of course of paramount importance. The confirmation, or final diagnosis, is made either by surgical biopsy or autopsy examination.

The important clinical features of the 14 cases is summarized in the following:

The age incidence varied from 29 to 67 years, averaging 42 years. Sixty-four per cent were men, and all were of the white race. Eighty-five per cent had evidence of increased intracranial pressure, either papilledema, elevated spinal fluid pressure, or both; 8 of the patients had convulsive seizures, either focal or generalized, while in 1 case the history of convulsions was questionable. Either before or after operation the recent growth of a skin

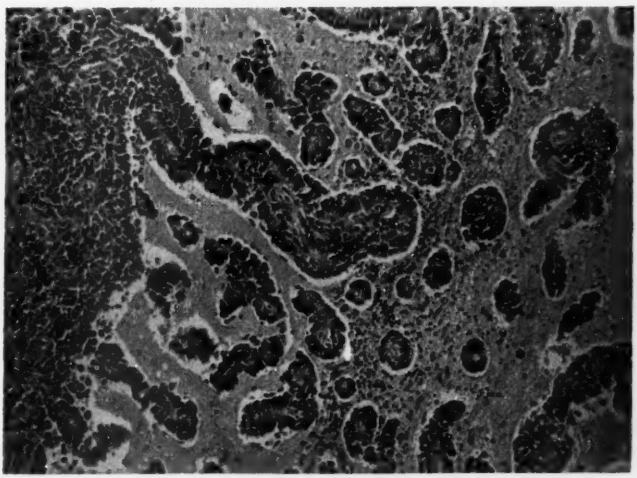


Fig. 9. Case 2. Secondary malignant melanoma. Perivascular cuffs of tumor cells about cerebral vessels near metastatic nodule.

mole was related in 9 of the group and 7 patients had previous excision or cauterization of a pigmented nevus. The skin was known to have been the primary site in 9 patients, the left eye in 2, and in 3 the site of the primary lesion was not known. The onset of vitiligo, with depigmentation of the eyelashes and hair over the chest (fig. 7) coincided with the onset of headaches in 1 case. Melanuria was found in 2 of the 3 cases in which attempts were made to identify melanin in the urine; the spinal fluid showed a negative test for this pigment in the 4 where it was sought. Xanthochromic spinal fluid was present in 5 of the patients. The spinal fluid protein was 50 mg. or greater in 8 of the 11 cases in which it was determined. Chest roentgenograms were reported normal in 8, one showed evidence of metastases, the diagnosis of metastasis was questionable in another, and there was one instance in which the chest was normal on first examination but showed metastatic lesions 4 months later; no record of chest x-ray examination was found for 3 patients.

Surgical therapy fails to cure the patient, and x-ray therapy is valueless.

Summary and Conclusions

Pigmented tumors of the central nervous system are presented as 3 entities; pigmented meningioma, primary leptomeningeal melanoma, and secondary malignant melanoma.

An example of a pigmented meningioma is described with the histologic diagnosis made on re-examination of the surgical specimen 6 years following the first and erroneous diagnosis of melanoma. If this unusual tumor had not been pigmented, it most likely would have been identified by the surgeon as a meningioma or neurilemmoma, but the inclusion of melanin pigment by the tumor cells made confusion with the melanomas certain.

A single example of primary leptomeningeal melanoma is briefly presented in which the patient had an associated extensive pigmented cutaneous nevus. Either the association of the cutaneous and neural lesions was a coincidence, or the cutaneous and neural lesions were related congenital malformations as part of a developmental ectodermal disturbance.

Fourteen cases of secondary malignant melanoma are discussed. Attention is called to the importance of melanotic neural metastases. This likelihood should constantly be considered in the differential diagnosis of cerebral neoplasm.

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RENAL MECHANISMS IN MAINTENANCE OF FLUID AND ELECTROLYTE BALANCE

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MAINTENANCE of fluid and electrolyte balance by the kidney implies a conservation at normal levels of the volumes, osmotic concentrations, compositions, and reactions of both extracellular and intracellular fluids. To do this the kidney must have means of adjusting appropriately to all possible stresses of diet and disease. The fluid in contact with the kidney and capable of modifying its functions directly is the blood. Consequently, appropriate renal mechanisms are responsive to changes in blood volume, in osmotic or water concentration, to changes in electrolytes, and also to blood pH.

The nephron, the unit of renal structure which subserves these varied functions, is a composite of vascular and epithelial tissues. The vascular element comprises the afferent and efferent arterioles, and the glomerular and peritubular capillaries. This element is concerned with the rate of renal blood flow, the volume of fluid filtered from the blood through glomerular capillaries and with picking up the fluids reabsorbed by the tubules and restoring them to the circulating systemic blood. The epithelial portion acts on the one hand by selective reabsorption of substances from tubular fluid and on the other by the secretion into it of certain specific materials.

The function of renal maintenance has been summarized by Homer Smith in the axiom that "the composition of blood and body fluids is determined less by what the mouth ingests than by what the kidneys keep." This "keeping" involves both the vascular and the epithelial portions of the nephron. The vascular portion is primarily concerned with adaptation to volume change and the epithelial portion with adaptation to changes in composition and reaction (Table 1).

As concerns volume, a decrease in body fluid usually involves shrinkage of blood volume and, ultimately, a decrease in cardiac output. Whenever cardiac output becomes less than is required for concurrent metabolic needs, there results renal vasoconstriction. This vasoconstriction reduces the rates of renal blood flow and of glomerular filtration. It usually is associated with oliguria and increased sodium reabsorption. Similarly, an abrupt increase in plasma volume and cardiac output, such as can be initiated by injection of hypertonic saline or salt-poor albumin, elicits renal vasodilation, increased glomerular filtration and diuresis. Since, at their outset, these adjustments do not modify the renal epithelium, they are spoken of as "prerenal" or extra-renal," which, of course, they are not. They are "pre-tubular" only.

Table 1

MECHANISM	AFFECT	DISEASE
1. Vascular	Volume	Shock Heart failure Dehydration
2. Epithelial	Composition water	Diabetes insipidus
	Na, K, Cl	Fluid losses Addison's Nephropathies
	Reaction (pH)	Acidosis Alkalosis

Vasoconstriction in response to a decrease in cardiac output is teleologically useful when, as in early shock, the net result is a deviation of as much as 20 per cent of the cardiac output from the kidney into the more immediately vital channels of the liver, heart, and brain. The oliguria and sodium reabsorption tend to restore the volume of interstitial fluid and thus also to maintain tissue pressure and support an endangered circulation. However, when renal vasoconstriction is excessive and unduly prolonged, the ischemic renal tubules become damaged and the stage is set for one of the many forms of nephron nephrosis, such as crush syndrome. Thus, what at the outset was life-preserving may in the end become lethal. In contrast, in congestive heart failure, where cardiac output is also less than concurrent bodily need, vasoconstriction and retention of fluid in blood and tissue spaces is damaging from the start.

The tubular mechanisms of maintenance proceed in two phases. The first "obligatory" phase consists in reabsorption of water and electrolyte from tubular fluid through the cells of the proximal convoluted tubule. This function accounts for the vast bulk of reabsorbed water, sodium and chloride. It is relatively invariant except as it is altered by changes in filtration rate. Consequently, "obligatory" reabsorption is hardly germane to this discussion. Rather, we are concerned with the residual reabsorptions and excretions which are "facultative" and which vary in response to changes in composition and reaction of body fluids (Table 2). These facultative adjustments are principally made in the distal convoluted tubule.

The first of these mechanisms is concerned with the osmotic concentration of water content of body fluids. The control depends on the responsive-

ness of the postpituitary and hypothalamus to changes in the water concentration of the blood. A decrease in concentration due to water loss or to solute excess causes liberation of posterior lobe hormone. This acts on specific distal tubular cells to increase reabsorption of water. The result is antidiuresis and excretion of hypertonic urine. Failure of this function at the pituitary level results in diabetes insipidus. Failure at the renal level underlies the fixation of specific gravity and hyposthenuria found in renal disease.

Control of discrete electrolytes, as contrasted with the mass osmotic control, depends in large measure on responses of the adrenal cortex. Its steroids of the desoxycorticosterone series act on the tubular epithelium to increase reabsorption of Na and to increase excretion of K. They are probably liberated in response to a decrease in the ratio of Na/K in the plasma. Loss of secretory function in the adrenal, as in Addison's disease, results in Na depletion and K retention in the blood. Impairment of responsiveness to the hormone in the renal tubules underlies the pseudo-Addisonian syndrome of "salt-losing" nephritis. This phenomenon is seen in advanced chronic glomerulonephritis and also during the onset of diuresis in patients with acute nephron nephroses whose tubular epithelium has just begun to regenerate. It is important to note that the normal mechanism for sodium retention is especially active, so that sodium all but disappears from the urine during sodium depletion. The mechanism for potassium retention is not nearly as adequate. Potassium can continue to be lost in the urine in spite of a potassium deficit and hypopotassemia results.

In contrast to these renal mechanisms with associated extrarenal controls, the renal regulation of the reaction of body fluids is vested wholly in the kidney. It depends on the ability of tubular cells to change the rates of

Table 2

OBJECT	MEANS	CHANGE
Volume	Cardiac output Vasomotor (?)	Blood flow Glomerular filtration
Composition osmotic (water)	Post. pituitary	Water reabsorption
Discrete ions	Adren. cortex	Reabsorption and secretion of ions
Reaction	Renal tubules	NH_4^+, H^+ secretion Na^+ HCO_3^- reabsorption

secretion of ammonium and hydrogen ions on the one hand and of reabsorption of sodium ion on the other. Acidosis (perhaps most effectively that due to accumulation of beta-hydroxybutyric acid) stimulates formation of ammonia from amino acids and glutamine. Ammonium ion then passes into the tubular fluid where it is exchanged for sodium ion which is reabsorbed together with bicarbonate. Simultaneously, hydrogen ion (H^+), formed in the cell by decomposition of carbonic acid (H. HCO_3), is secreted into the tubule and exchanged for sodium ion, so that Na HCO_3 is restored to the blood. Consequently, in acidosis the urine is rich in ammonia acid and sodium-poor. Conversely, alkalosis depresses ammonium formation and also the rates of sodium and hydrogen ion exchange, so that the urine becomes ammonia-poor, alkaline, and rich in sodium. Failure of the mechanisms of ion exchange because of renal tubular disease accounts for much of the base depletion and acidosis seen in terminal glomerulonephritis.

When, as is common, the primary defect in any of these mechanisms is renal, the various aspects of ineffective maintenance tend to be concurrent and the changes in body fluids multiple and mixed. Thus, in acidosis with dehydration, the mechanism of renal failure is predominantly hemodynamic. But in hyponatremia and dehydration associated with severe alkalosis, as in gastric vomiting, the distal tubules may necrose. The resultant nephron nephrosis conjoins tubular epithelial and vascular hemodynamic mechanisms.

Failure of these mechanisms cannot be corrected by rule of thumb. Effective treatment demands a consideration of the mechanisms at fault and correction or replacement on physiologic principles.

SACRAL PERINEURIAL CYSTS

With Case Report

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THE diagnosis of a sacral perineurial cyst may be difficult to establish because of the location caudad to the tip of the dural sac and because the cysts do not communicate with the subarachnoid space. Spinal fluid manometrics and analysis, as well as intradural contrast myelography, have proved of no value. The progressive development of a clinical picture pointing to the sacral portion of the cauda equina is perhaps the best indication. The entity should be suspected and searched for in the occasional patient when, at laminectomy for sciatica, the protruding disk is not disclosed.

The patient described showed clinical findings of a lesion compressing the sacral portion of the cauda equina which was found at operation to be an extradural cyst.

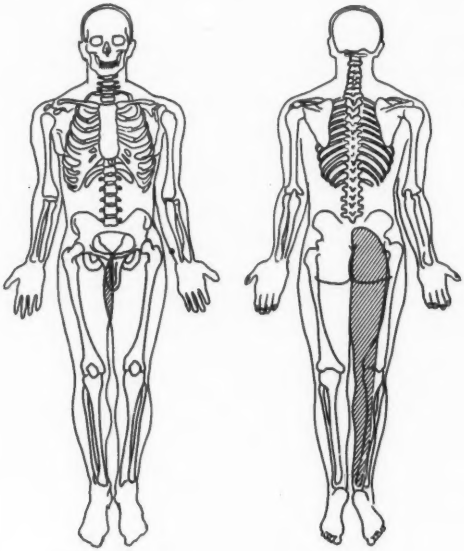

Fig. 1. Sensory deficit in right saddle area starting with S_2 dermatome. (Author's case).

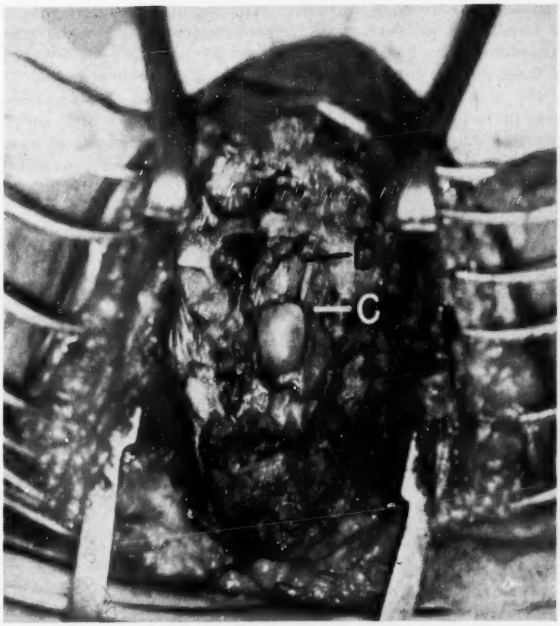

Fig. 2. Operative exposure showing tip of dural sac (d) with perineurial cyst (c) presenting just below.

Case Report

A 40 year old white housewife was first seen in the Department of Urology at the Cleveland Clinic in August, 1949 because of headaches and urinary retention. Four years previously she first experienced increasing frequency, nocturia, and a suprapubic bearing-down sensation when reclining. There had been hesitancy, small urinary stream, and even with straining, incomplete emptying of the bladder. In November 1949, complete retention of urine developed. The patient was hospitalized elsewhere for 10 days for repeated catheterization, after which she was able to void with difficulty. Three days before admission complete retention again occurred. During the past 3 months she had progressive occipital and retro-orbital headache, more severe when reclining. In the past 2 months a dull, aching pain in the anterior aspect of the right and then the left thigh appeared, as well as a deep, steady, sacral backache, both of which were intensified when in the supine position.

On admission, she was found to have 600 cc. of residual urine without, however, the expected bladder neck obstruction. Neurologic examination (fig. 1) was completely negative with the exception of a relative right saddle hypalgesia extending down the posterior aspect of the right leg in the second sacral dermatome. The patellar and Achilles reflexes were equal and active. Jugular compression caused mild increase in the sacral backache. Lumbar puncture, performed at the lumbosacral interspace, revealed clear, colorless cerebrospinal fluid with normal hydrodynamics. The fluid contained 1 cell per cu. mm., a negative Pandy reaction, 33 mg. total protein, and negative Wassermann, Kahn, and colloidal gold reactions. A roentgenogram of the lumbosacral spine revealed no abnormalities.

Pelvic examination was normal. The patient was slightly obese, weighing 151 pounds, and was 5′ 3″ tall. Blood pressure was 110/80. The remainder of the general physical examination was satisfactory. Blood sugar level was 99 mg. per cent, 5-¾ hours postprandially, and the urea, 21 mg. per cent.

In view of the sensory changes, a lesion compressing S-2 was suspected and sacral laminectomy was performed on September 9, 1949. The Hudson drill with a large burr was used to penetrate the posterior sacral plate at the lower border of the S-2 segment, slightly to the right of the midline. As the bone was penetrated, a thin, translucent, tense, cystic membrane bulged through the opening. No epidural fat was visible. Rongeurs were used to enlarge the bony exposure to include the second sacral lamina, the lower half of the first, and the upper half of the third sacral segments. In the cephalad portion of the exposure (fig. 2) the caudal end of the dural sac was visualized with the normal epidural fat around and below except where the clear, cystic structure was apparent. The dural sac pulsated normally although the cyst did not. The dural sac was easily collapsed by gentle pressure; the cyst was extremely tense and unyielding. When the head of the table was lowered the dural sac collapsed, but the cyst remained tense. A hypodermic needle was introduced into the cyst and clear fluid obtained. The cyst was then removed carefully by dissection and appeared to originate from a small nerve filament in the exact midline arising at the extreme tip of the dural sac in the region of the filum terminale. The removal of the cyst left a concave bed formed by compressed right sacral nerve roots. Hemostasis was assured and the incision was closed in the usual manner.

By the third postoperative day the patient was voiding spontaneously and the saddle hypalgesia was diminishing. She was discharged on the ninth postoperative day, at which time there was complete relief of all subjective urinary symptoms. The hypalgesia extending into the right leg and in the right saddle area could not be elicited.

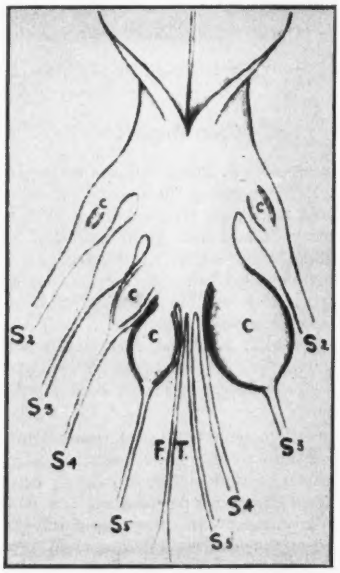

Fig. 3. Composite drawing showing position and size of cysts at cadaver dissection. From Tarlov, I. M.: Arch. Neurol. and Psychiat. 40:1067 (Dec.) 1938.

She was last examined 3½ months after operation, at which time she stated that the headaches, urinary symptoms, leg and low back pain had been completely relieved. However she still retained a small amount of residual urine which diminished at each succeeding examination. Neurologic examination revealed only normal findings.

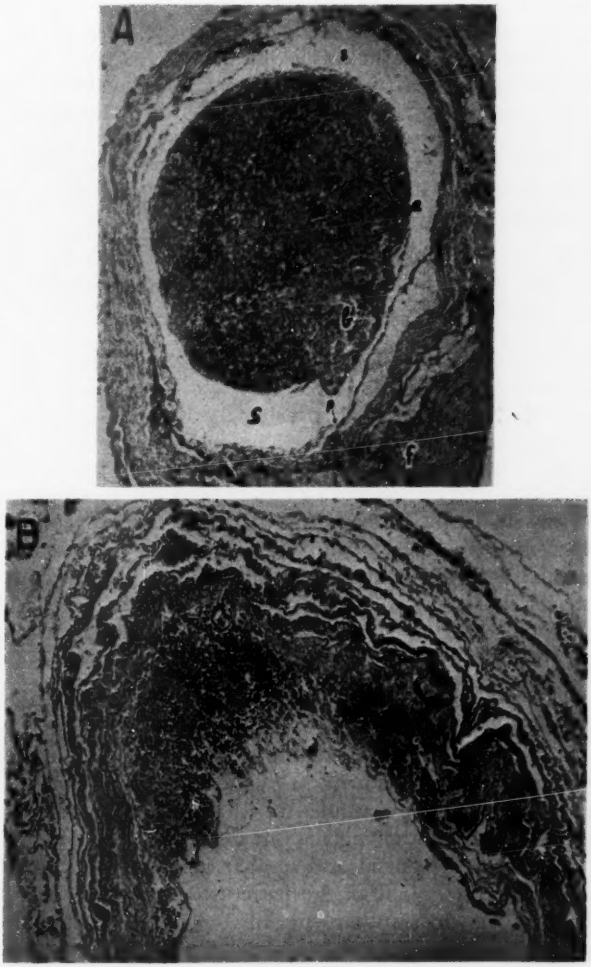

Fig. 4. (a) Cyst beginning in the perineurial space (S) between the endoneurium (e) and the perineurium (P). Epineurium (f) surrounds the perineurium (x-35). From Tarlov, I. M.: Arch. Neurol. and Psychiat. 40:1067 (Dec.) 1938; (b) Author's case showing analagous microscopic appearance to Fig. 4a (x-70).

Discussion

One other case report of a similar lesion has come to my attention. In 1948, Tarlov[1] described a perineurial cyst attached to the posterior root of the right second sacral nerve in a 42 year old woman with sciatica. This patient exhibited a reduced lumbar lordosis, local pain on pressure over the fifth lumbar spinous process, pain down the posterior aspect of the right leg on hyperextension and right lateral flexion of the back, weakness of dorsiflexion of the toes, hypalgesia along the outer aspect of the dorsum of the right foot, and an absent right Achilles reflex. When the expected disk protrusion was not found at operation, his attention was called to an extrusion of fat from beneath the lamina of the sacrum. Further exposure disclosed the cyst. With its removal the patient experienced prompt relief of symptoms and rapid clearing of neurologic signs.

Interest was first focused upon this pathologic entity by Tarlov[2] in 1938 during dissection studies of the filum terminale. In 30 autopsies performed upon adults with no correlated symptoms, he found 5 instances of cysts attached to the posterior sacral or coccygeal nerves (fig. 3) or nerve roots on the extra-dural portion of the filum terminale. These cysts were neither parasitic nor neoplastic, and appeared first as a space developing between the continuation of the arachnoid covering the root, the perineurium, and the endoneurium – the underlying pial extension surrounding the nerve fibers (fig. 4a). Foci of lymphocytes and plasma cells are frequently present in the outer perineurial cyst wall as well as an increased number of relatively large blood vessels. In his study of the literature, Tarlov was able to find only 2 earlier articles; one, by Marburg,[3] describing 4 cysts of the spinal ganglia, and another by Hinrichs[4] reporting 1 case in which 3 cysts occurred on the posterior thoracic and lumbar roots near the ganglia. None of these autopsy cases had correlated symptoms, and the exact site of origin was not reported.

The incidence of these cysts is not as uncommon as the paucity of reports would indicate. Tarlov recorded 5 cases in which cysts were found out of 30 cadavers dissected, and 3 similar conditions in 39 later dissections.[5] Rexed[6] at the Karolinska Institute in Sweden has recently reported 8 instances out of 17 specimens examined in which he found arachnoidal proliferations with severe cystic changes at one or several levels of both posterior and ventral roots in the dorsal and lumbar areas at their entry into the intervertebral foramina. None of the patients from whom these specimens were derived had shown symptoms suggestive of the pathology found. The microscopic sections from this material showed a close resemblance to those described previously by Tarlov except for the additional findings of arachnoidal proliferation. These findings suggest that some patients with radicular pain at various levels presenting diagnostic problems have perineurial cysts. Further correlation of clinico-pathologic data in this regard is needed.

Summary

Sacral perineurial cysts are relatively common and can produce symptoms. The 2 cases discussed suggest that this condition should be suspected more often. When the diagnosis is made surgery offers good possibilities for complete relief of symptoms.

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DISORDERS OF URINARY TRACT

(In March 1949 the Frank E. Bunts Educational Institute presented a continuation course on Diabetes, the proceedings of which were later published in the Cleveland Clinic Quarterly. These proved so popular that it has been decided to publish the proceedings of the similar course on Medical and Surgical Disorders of the Urinary Tract held on November 17, 18, and 19, 1949.—Ed.)

PYELONEPHRITIS AND GLOMERULONEPHRITIS

Robert D. Taylor, M.D.

Both pyelonephritis and glomerulonephritis can cause proteinuria, pyuria, hematuria, cylindruria, and eventually hypertension and renal failure. Glomerulonephritis has been more widely studied and hence, in spite of an incidence of only 0.7 per cent, is a more common diagnosis in the presence of abnormal urinary findings than is pyelonephritis which was observed in 5.6 per cent of 3607 postmortems. Glomerulonephritis is a relentlessly progressive disease while pyelonephritis can be cured or controlled.

Clinical Differential Diagnosis

A. Chronic Pyelonephritis	B. Chronic Glomerulonephritis
1. History	1. History
More common among women; often follows marriage or pregnancy. Recent or remote history of chills, fever with dysuria. Nocturia is more frequent during active phase. Edema is rare save in terminal state.	There is no sex predominance. There is sometimes history of acute hemorrhagic glomerulonephritis. More often proteinuria is discovered during routine examination. Edema is frequent. Nocturia gradually increases and becomes continuous.
2. Physical Findings	2 Physical Findings
Patients may appear acutely or chronically ill. Blood pressure is usually normal and becomes elevated only as renal failure supervenes; occasionally acute hypertension is present. Costovertebral angle tenderness is demonstrable. No edema. Fever is common and may be of septic type.	Unless the process is acute or terminal, patients appear well. Blood pressure is often normal, commonly moderately elevated early in course; high in later phases. Dependent edema. Mucous membranes and skin appear moderately pale. Fever rare, due to intercurrent infection or massive edema.

Laboratory Findings

1. Addis Test	1. Addis Test
a. Tubular Function	a. Tubular Function
Ability to concentrate urine is usually fairly well preserved. If depressed, the change is proportionate to decrease of glomerular filtration. Concentrating ability may improve with treatment.	Until advanced and terminal phases, concentrating power moderately depressed. Not impaired in proportion to filtration rate. (Measured from urea clearance)

b. Proteinuria

Usually not more than 1 to 2 Gm. per 24 hours.

c. Cylindruria

May be excessive during active inflammation and remittent at intervals. Casts are usually granular or cellular. (Leukocytes)

d. Hematuria

During active infection may be considerable. Clears with treatment.

e. Pyuria

May be severe. Leukocytes show pronounced cytoplasmic motion (vital stain or phase microscope).

2. Urea Clearance

a. Filtration Rate

Moderately depressed and in proportion to tubular damage.

b. Blood Urea

May be elevated to 50 to 60 mg. per 100 cc. in spite of adequate filtration because of fever-induced, excess protein catabolism.

3. Blood

a. Hemoglobin

Normal or depressed if disease is longstanding.

b. White Cells

Often moderate leukocytosis.

c. Proteins

Usually normal.

4. Urine

a. Culture

May at times be sterile, but the same organism can usually be recovered on repeated culture.

5. X-rays

In primary pyelonephritis, kidney pelves,

b. Proteinuria

Usually above 2 Gm. per 24 hours, commonly 4 to 10.

c. Cylindruria

Casts are constantly increased in number and until terminal are predominately hyaline; if cellular, show red cells and epithelium.

d. Hematuria

Varies in degree but is almost constantly present.

e. Pyuria

Moderate. Leukocytes inert.

2. Urea Clearance

a. Filtration Rate

Excessively depressed, more so than tubular function.

b. Blood Urea

May be normal in spite of depressed clearance.

3. Blood

a. Hemoglobin

Early—normal. With appearance of azotemia—progressive anemia.

b. White Cells

Normal.

c. Proteins

Albumin fraction often low.

4. Urine

a. Culture

Sterile.

5. X-rays

Normal.

ureters and bladder have normal shadows until late in the disease. Then blunting of calyces and distortion of pelves may appear. In secondary types an obstructive lesion is demonstrated by intravenous or retrograde pyelograms.

Treatment	**Symptomatic**
1. Selection of proper antibacterial drug.	1. Alphalin.
2. Proper follow-up.	2. Potassium citrate.
	3. Thiocyanate.
	4. Low sodium diets.
	5. Adequate fluid intake.
Results	
Cure or arrest of disease.	Progressive renal failure.

TECHNIC AND SIGNIFICANCE OF ADDIS COUNT AND UREA CLEARANCE

Harriet P. Dustan, M.D.

Because urea is always present in blood and urine and because the methods for its measurement are not too exacting, simultaneous estimates of blood and urinary urea have been used for a long time as tests of renal function. The most practical of these tests is the urea clearance of Van Slyke. In principle, the test measures the volume of blood equivalent to one minute's urinary excretion of urea. The formula used in its calculation expresses this ratio as UV/B, for "maximum" clearance at high urine flows (C_m; normal 75 cc./min.) and $U\sqrt{V}/B$ for "standard" clearance at urine flows of less than 2 cc. per minute (C_s; normal 55 cc./min.). For convenience in interpretation, the values are reported as per cent of normal by multiplying observed C_m by 1.33 and observed C_s by 1.85.

The disparity between C_s and C_m results from the diffusion and reabsorption of urea from the tubular fluid. At rapid, steady, or slowly decreasing rates of urine flow, the proportion of urea reabsorbed is constant at about 40 per cent of that filtered. Consequently, changes in urea clearance can be interpreted in terms of changes in glomerular filtration. Variations in reabsorption of urea incident to the onset of diuresis, to exercise, pain or inadequate hydration, disturb this relationship and render the test uninterpretable.

From the Addis examination, one obtains three types of information: (1) the ability of the kidney to concentrate urine in response to water deprivation as indicated by the nonprotein specific gravity, (2) a quantitative determination of urinary protein, and (3) a quantitative determination of the numbers of casts, red cells, white cells, and renal epithelial cells in the urinary sediment.

The patient is deprived of water for a 24 hour period, and the determinations are made on the urine collected during the last 12 hours of water deprivation. Normally, the nonprotein specific gravity of this specimen will be 1.026 or above. If the patient misunderstands the instructions and takes fluids, if he has congestive cardiac failure or increased extracellular fluid from any cause, or if he has been on an exceedingly low-protein intake such as a rice diet, a falsely low value will be obtained. In a test in which

these conditions are not present, the nonprotein specific gravity is a reliable indication of tubular integrity.

Normally, the urine contains less than 0.2 Gm. of protein in 24 hours. In diseases which increase the permeability of the glomerular capillary membrane, there is an increase in urinary protein. The cells and casts of the urinary sediment can be considered as a renal biopsy. The quantitative estimation of components of the sediment is exceedingly valuable, not only in diagnosis but in following the course of renal disease.

RENAL DISEASE OF HYPERVITAMINOSIS D

Leonard L. Lovshin, M.D.

I. **Introduction**
- A. Vitamin D intoxication becoming more common with the increased use of high potency preparations.
- B. Used chiefly in the treatment of arthritis, sarcoid and lupus vulgaris.
- C. No good evidence that Vitamin D is useful in the treatment of arthritis.
- D. All forms of Vitamin D probably can cause intoxication.
  1. Whittier process (Ertron) has caused intoxication in many instances.
  2. Excess cod liver oil in children.

II. **General Aspects of Hypervitaminosis D**
- A. Dosage.
  1. Individual variation.
  2. May occur with therapeutic doses as small as 100,000 units daily.
- B. Symptoms—nausea, vomiting, anorexia, weakness, malaise, polydipsia, polyuria, headache, diarrhea, weight loss.
- C. Objective Findings.
  1. Signs of renal damage.
  2. Metastatic calcification—arterial, around joints, renal.
  3. Anemia common; may be out of proportion to the amount of renal failure.
  4. Increased blood calcium; normal blood phosphorus; increased urinary calcium.
- D. Mechanism.
  1. Many of toxic symptoms may be due to hypercalcemia. (Increase of ionized portion)
     a. Similar picture in hyperparathyroidism.
     b. No clinical symptoms with multiple myeloma. (Increase in protein-bound fraction)
  2. Theory that cellular damage is due to the metastatic calcification. (Ham)
  3. Theory that cellular damage precedes calcification. (Steck)

III. **Renal Disease in Hypervitaminosis D**
- A. Kidney damage the most constant feature. May be easily missed because of paucity of urinary findings.
  1. (Howard and Meyer)—Series of 10 cases; all showed signs of some renal failure.
  2. (Schneider and Kammer)—Series of 9 cases; all 9 had renal disease.
- B. Clinical Findings.
  1. Slight to moderate albuminuria; usually below 0.5 Gm. per liter.
  2. Occasional granular casts.
  3. Elevated blood urea.
  4. Loss of concentrating power.

5. Decreased urea clearance and P.S.P. excretion.
6. Picture most resembles old chronic pyelonephritis or nephrosclerotic kidney.

C. Pathologic Findings.
1. Calcification in renal tubules—either in lumens or tubular cells.
2. Arterial calcification.

D. Prognosis.
1. Renal damage reversible if found early.
2. Amount of residual damage depends on amount of fibroblastic proliferation around calcium.
3. Renal damage persisting over 6 months after discontinuance of Vitamin D is usually permanent.
4. In Howard's series of 10 cases only 2 returned to normal.

E. Treatment.
1. Discontinuance of Vitamin D.
2. Force fluids—3000 to 4000 cc. per day.
3. Low calcium diet.
Because symptoms often suggest primary gastrointestinal disease, patients are often on milk diet. (High calcium)

IV. **Analysis of 12 cases at Cleveland Clinic**

A. Blood calcium elevated in all 12. Range 11.9 to 15.5 mg. per cent.
B. Blood phosphorus elevated in 4. Highest 6.1 mg. per cent.
C. Blood urea elevated in 11 of 12.
D. Urea clearance definitely decreased in 10 of 11 determinations.
E. Anemia in 10 of 12. (Below 11 Gm. hemoglobin)
Red blood cells below 4,000,000 in 9; on 4 occasions below 3,000,000.
F. Albumin in urine in 10 of 12. (1 and 2 plus)
Addis determinations in 5; protein was below 0.5 Gm. per liter in all.

MYELOMATOSIS, PERIARTERITIS, AND LUPUS ERYTHEMATOSUS

Donald W. Bortz, M.D.

In multiple myeloma the renal lesion may be manifest by proteinuria or, most commonly, albuminuria, hematuria, elevation in blood pressure, impaired renal function and edema. Renal insufficiency is invariably present at some stage of the disease and most commonly appears as part of the terminal picture as manifested by an elevated blood urea. The alteration in serum proteins as is usually noted in a high total serum protein is not actually the result of any structural kidney lesion, but is usually attributed to the fact that plasma cells serve as the origin of the increased amount of serum protein. One of the most common, and certainly the most characteristic laboratory observation in multiple myeloma is the presence of Bence-Jones protein in the urine. This protein precipitates at a relatively low temperature, usually 50 to 60 C and is partially or completely dissolved at 100 C, the precipitate reappearing upon cooling. It is usually present in 60 to 70 per cent of all cases of myelomatosis, but may occasionally be seen in myelogenic osteosarcoma, carcinomatous metastases to the bone marrow, and rarely in leukemia. Dr. Lena Lewis in our laboratories has studied the Bence-Jones protein in the urine by electrophoretic methods and has noted a usually constant change.

Pathologically, the kidneys are of normal size, unusually pale and firm to the touch. They present a characteristic pattern of protein deposition. Not infrequently, deposits of calcium, presumably resulting from the osteolytic bone lesions, may be seen in the

convoluted tubules. The tubules may also be dilated, but this dilatation occurs only at the site of either the protein or the calcium deposition.

The diagnosis of periarteritis nodosa, now being made with increasing frequency ante mortem, must always be entertained when the urine shows hematuria or at least the presence of erythrocytes microscopically, albuminuria, cylindruria and an elevation of the blood urea.

Periarteritis involves the medium sized arteries and arterioles and in the acute phase may involve one or all coats of the vessel. A large number of polymorphonuclear leukocytes and eosinophils present in the acute phase become replaced by a predominance of lymphocytes and monocytes as the chronic phase of the disease is reached. Characteristically the involvement of the vessel is usually segmental in nature. The changes are within the vascular bed whereas the usual changes in myeloma are secondary to protein deposition in the tubules.

Although Bence-Jones proteinuria is never observed, albuminuria, cylindruria, and erythrocyturia are all present in the urine of the lupus suspect. An increase in the cellular contents of the Addis count, which may be noted in any of the diseases under discussion, is present also in lupus erythematosus, although these changes are never as severe as those observed in the typical nephritides. Just as in myelomatosis, albuminuria is invariably present at one time or another in the disease. It may be associated with hematuria or cylindruria. While terminally an acute infectious process may intervene, evidences of renal failure as manifested by an elevation in the blood urea may occur. *All changes in this disease are secondary to the involvement of the connective tissues of the body.*

It is only by combining the information from the clinical laboratory with that obtained from the clinician's examination that the presence of any of these entities may be suspected. Confirmation of the clinical diagnosis awaits the pathologist; deposition in the tubules of the kidney in myelomatosis; arterial or arteriolar involvement in periarteritis nodosa; and the typical connective tissue changes of lupus erythematosus.

MANAGEMENT OF URINARY TRACT INFECTIONS INCLUDING TUBERCULOSIS

Eugene F. Poutasse, M. D.

With the advent of new chemotherapeutic drugs the treatment of urinary infections has become much more effective, provided that certain fundamental principals are adhered to.

1. A large number of uncomplicated cases of urinary tract infection will clear up readily with fairly simple treatment.

2. Any serious, recurrent, or persistent infection should be carefully investigated for stone, obstruction, anomaly, or other lesions acting as a source of infection, and treated as indicated.

3. A Gram stain of fresh urinary sediment gives immediate and valuable information regarding type and degree of infection. Cultures should be made in all cases. In serious infections the organism should be tested for sensitivity to various antibiotics to determine the most effective agent.

4. Several drugs are available for the treatment of urinary tract infections. The development of bacterial resistance, which applies particularly to streptomycin, should be distinguished from innate ineffectiveness of a given antibiotic against a specific type of bacteria.

Mandelic acid is a cheap, effective agent against B. coli and Streptococcus faecalis provided urine is maintained at a pH of 5.5 and the concentration in the urine is about

1 per cent. The sulfonamides act best in alkaline urine and are useful against coliform bacteria, but toxic reactions must be watched for. Sulfisoxazole (trade name gantrisin) may prove useful in controlling proteus infections, particularly when combined with chloromycetin. Penicillin, aside from being the drug of choice against the Gram negative gonococcus, is useful only for Gram positive organisms. Dihydrostreptomycin, highly effective against Gram negative organisms, must be used only when urine is alkaline, as resistant variant strains develop more readily in acid urine and limit its usefulness.

Aureomycin and chloromycetin have a similar wide rapid bacteriostatic action against both Gram negative and positive organisms. Therapeutic dosage varies considerably with the degree of infection.

5. The pathogenesis of genitourinary tuberculosis must be thoroughly understood. The use of long term streptomycin therapy is gradually evolving and must be integrated with appropriate surgery as indications arise. New drugs to be used either with or without streptomycin are under investigation.

	Mandelic Acid	Sulfa	Penicillin	Streptomycin	Aureomycin	Chloromycetin
B. coli	+	+		+	+	+
Streptococcus faecalis	+		±		+	+
Staphylococcus albus			+		+	+
Proteus vulgaris		gantrisin ±				±
Pyocyaneus				±	±	
Aerobacter aerogenes				+	+	+
Diphtheroids			+		+	+
Alcaligenes faecalis		+			+	+

This table illustrates the effective antibacterial activity of the drugs discussed.

CRUSH SYNDROME

A. C. Corcoran, M.D.

The term "crush syndrome" is restricted to that form of lower nephron nephrosis which follows trauma of the type experienced during urban bombing. The lesion, as in other forms of this condition, is characteristically one of obstruction and necrosis of distal convoluted tubules with proximal damage also. Clinical course is one of oliguria or anuria with the onset of diuresis delayed for 10 to 14 days, during which time death may result from potassium intoxication. After this time the course is toward recovery. The onset of diuresis probably coincides with adequate regeneration of renal epithelium.

Mechanism of the condition illustrated by studies on animals evidently involves

multiple factors: (1) renal vasoconstriction, (2) oliguria and aciduria, and (3) excretion of hemoglobin pigment.

Treatment: (1) Preventive: block of afferent impulses, vigorous treatment of shock and hypotension, pressure bandaging and establishment of diuresis; (2)Supportive: see Management of Acute Anuria.

UNILATERAL RENAL DISEASE AND HYPERTENSION

Robert D. Taylor, M.D.

The concept of unilateral renal disease and hypertension as a syndrome had its inception following the report of Goldblatt and his associates that a constricting clamp applied to the renal artery of dogs caused persistent arterial hypertension. It was given further support when Page produced arterial hypertension by cellophane-induced perinephritis. In spite of the appeal of this concept as a cause of human arterial hypertension, too frequently nephrectomy has no effects upon the blood pressure of hypertensive human beings. However, an occasional patient has disease of a single kidney that produces hypertension.

If signs of unilateral renal disease exist, final decision about nephrectomy must be empirical and depend upon knowledge gained from animal experiments and the nephrectomies done over the past 15 years.

In rats, experiments of but a few weeks duration have shown that removal of the kidney causing hypertension is followed by return of the blood pressure to normal. However, after months and years of hypertension, little change in blood pressure occurs after nephrectomy. Experience has been similar among human beings. Those benefited by nephrectomy have been children or patients with a short history of hypertension.

The chief indications for nephrectomy are those which would lead to operation whether or not hypertension was present. Exceptions occur, however. If the presence of unilateral renal disease can be established in a patient who gives no family history of hypertensive disease, the chances are greater that his hypertension is due to the acquired lesion than among those patients who have a strong familial background. Furthermore, nephrectomy may be justified if there is little or no arteriolar disease, which indicates that the affection is probably of comparatively short duration.

CYSTIC DISEASES OF THE KIDNEY

William J. Engel, M.D.

There are several different forms of renal cysts. (a) Polycystic disease occurs both in the newborn and in adults. (b) Multicystic disease of the kidney can be either congenital and unilateral or acquired and bilateral. (c) Simple serous cysts may occur either in solitary or multilocular form and either unilaterally or bilaterally. Among the rare types of cysts are: echinococcus; lymphatic; cystadenoma.

Polycystic kidneys are not rare, being found in about 1 out of 1000 autopsies and once in 3500 clinical urologic patients. There are two types of the disease: that occurring in the newborn which is usually fatal and the adult type which is more common and generally recognized in the third or fourth decade of life. Cause of polycystic kidneys is not known. Two prominent theories are failure of union of the collecting and secreting portions of the tubules or obstruction of the tubules. In any event, this is an hereditary disease with the basic fault probably lying in the germ plasm; it is always bilateral, producing multiple cysts which grow and multiply. The kidney becomes large, the

pelvis deformed, compression destroys the adjacent renal tissue, and death is usually the result of renal failure. Hemorrhages may occur into the cyst, infection is not uncommon, and cysts are frequently found in other organs such as the liver or lungs.

The most common symptoms are the presence of a bilateral abdominal mass, renal failure, hypertension, hematuria, or infection of the urinary tract. The urine generally contains albumen, red blood cells, and has a low specific gravity. The diagnosis depends on the performance of bilateral pyelograms. The kidneys are large with large pelves. There is variability of the calyces, dilation of the calyces, and circular indentations: The calyces are also elongated and stretched and variable in configuration. The pyelographic media show a variable density. The treatment is conservative and nonsurgical unless the cysts become large and painful, infected, with the presence of fever (and here antibiotics should be tried before surgery) or hemorrhage into the cysts. When operation is necessary, multiple puncture and drainage of the cysts is indicated.

Multicystic kidneys may be congenital and unilateral. They usually are recognized in children because of the presence of pain, chills and fever, persistent pyuria, and, rarely, a palpable mass. Surgical removal is the treatment of choice. In the adult form the cysts are more often bilateral and the etiology is probably tubular obstruction. There may be no clinical manifestations, but the condition should be suspected in the presence of unexplained azotemia, diminished renal function of obscure nature, and hypertension. The diagnosis is made by x-ray and pyelograms. Treatment is nonsurgical and is similar to that employed for other forms of renal failure.

Simple cysts, often called solitary, are either unilateral or bilateral. They are not connected with the pelvis, calyces, or ureter. They may be multilocular and grow to a large size. Complications of hemorrhage or infection are not unusual. Frequently there are no symptoms and the condition is found accidentally because of a palpable mass. Occasionally dull, indefinite, aching pain or acute symptoms of hemorrhage or infection are present. Treatment consists of simple aspiration or surgical removal. The cyst frequently does not recur following aspiration. Excision of the cyst or unroofing and packing, if it lies in the central portion of the kidney, may be advisable in some cases.

INTERCAPILLARY GLOMERULOSCLEROSIS

*Max Miller, M.D.**

In 1936 Kimmelstiel and Wilson first described a distinctive lesion of the renal glomeruli which they associated with a clinical syndrome of diabetes, hypertension, and a nephrotic syndrome. Since then the work has been confirmed by many investigators, the majority of whom have agreed upon the specificity of the lesion.

Although Kimmelstiel and Wilson described the lesion as consisting of hyaline thickening of the intercapillary connective tissue, in recent years careful studies have shown that it is really the result of profound focal thickening and hyalinization of the capillary loops or their basement membranes. "Intercapillary," therefore, is a misnomer.

The glomerular lesions are of two distinct types, the nodular and the diffuse. The nodular hyaline lesion is of a spherical shape and occupies the center of a glomerular lobule, varying in diameter from 20 to more than 100 microns. The second lesion consists of focal fibrosis of the majority of glomeruli without spherical hyaline masses. In many cases there may be definite transitions between these two types. The nodular lesions are almost pathognomonic of diabetes according to Ball and Lahipply.

The latter author has also emphasized the specificity of glomerular focal fibrosis for the diagnosis of diabetes pathologically. The focal fibrosis is present in nearly all the

glomeruli in an approximately equal degree in diabetes, as contrasted with the variation in degree and the presence of many normal glomeruli in nephrosclerosis, pyelonephritis, and glomerulonephritis. These lesions occur in from 30 to 60 per cent of diabetic patients, predominantly in the older age group. The longer the duration of the diabetes, the more frequently do the lesions occur and the greater the degree of involvement. Except for the study of Horn and Smetana all writers are agreed that it is present only rarely in other conditions. Thus Siegal found the lesions in only 1 of a series of 200 patients without diabetes and Laipply found 4 in 208 cases of various other types of kidney disease without diabetes.

Albuminuria is common in patients with typical glomerular lesions, being present in at least 80 per cent. When the lesions are severe, albuminuria is present in practically all instances. Contrary to Kimmelstiel's original description, the full nephrotic syndrome is relatively uncommon (6 per cent). However, when present, it is usually associated with severe glomerular changes. Renal failure may occur occasionally. Hypertension occurs frequently but probably no more so than in diabetic persons in the same age group without intercapillary glomerulosclerosis. Intercapillary glomerulosclerosis probably is not of too great significance because of the frequent lack of clinical manifestations. Nevertheless, it is important in that glomerulonephritis or nephrosclerosis need not be diagnosed in every diabetic patient who develops albuminuria.

*By invitation. *University Hospitals.*

RENAL LESIONS IN CHILDHOOD

William J. Engel, M.D.

Lesions of the kidney in children are similar to those in adults and methods of examination are identical; symptoms of renal disease should not be minimized. Persistent or recurrent pyuria, gross hematuria, incontinence, unexplained anemia, or a palpable abdominal mass should all be investigated from the urinary standpoint. Among the congenital anomalies, obstructions of the vesical neck and posterior urethra are common. These may produce bilateral renal damage. They should be recognized early and subjected to surgical correction as soon as possible. Ureterovesical obstructions are usually unilateral and result in hydroureter and hydronephrosis. Pain and chronic urinary infection are the usual complaints. A retrograde pyleogram or intravenous urogram should be used for diagnosis. Infection is combated with antibiotics and sulfa drugs. Surgical correction of obstruction is indicated. Hydronephrosis due to ureteropelvic obstruction is more often unilateral than bilateral. It may be caused by aberrant vessels, congenital stenosis, or periureteral bands and adhesions. Pelvioplasty to relieve the obstruction or nephrectomy, when a serious obstruction is present, are the indicated treatments. Ectopic ureter usually produces persistent pyuria and recurrent infection. Cystoscopic examination and retrograde pyelograms are indicated. The surgical treatment consists of heminephrectomy and removal of the infected ureter.

Renal tumors of the Wilms' type account for 20 per cent of childhood malignant tumors. The most common symptom consists of a tumor mass. Chills and fever and hematuria may occur. These tumors are rare in children over 10 years old. Treatment includes irradiation therapy and early nephrectomy when possible. The prognosis, however, is unfavorable.

Renal calculi are less common in children than in adults. The management, however, is similar. Cystinuria, an hereditary metabolic disorder, must be considered in children with renal colic and passage of stones. Nephrocalcinosis is uncommon in chil-

dren but is perhaps increasing in frequency. The most frequent symptoms are fatigue, anemia, anorexia, polyuria, and polydipsia. The significant laboratory findings consist of hyperchloremia, acidosis, azotemia, diminished renal function, and anemia. The x-ray reveals multiple pinpoint calcifications clustered at the renal pyramid. The pyelogram aids in localization.

THE NEPHROTIC SYNDROME

A. C. Corcoran, M. D.

The nephrotic syndrome (edema, gross albuminuria, hypoalbuminemia and hypercholesterolemia) occurs most often in chronic glomerulonephritis, not infrequently as part of the Kimmelstiel-Wilson syndrome, infrequently and only in children as true lipoid nephrosis; as a rarity it may be caused by secondary syphilis, leptospirochetosis or toxic nephrosis. It almost never occurs in chronic pyelonephritis.

The presenting defects are in protein and water-salt metabolisms.

Protein: The proteinuria is probably due to glomerular leakage with secondary hydrops of tubule cells due to protein stuffing. Albuminuria contributes to hypoalbuminemia, especially when diet is restricted, and thus to edema, but is not the sole cause of hypoproteinemia. The loss of *γ* globulin in urine, carrying with it complement and other antibodies, may explain some of the increased susceptibility to infections. A particular aspect of the protein defect is the hypoaminoacidemia associated with nephrotic crises. Proteinuria may of itself contribute to renal failure by obstruction of tubules; this is most likely where there is a large globulinuria. It is countered by urinary alkalinization with potassium citrate

Water: The edema is due in part to hypoproteinemia; it is also associated with a decreased ability to excrete salt and water. It is increased by NaCl and held in check by Na restriction. The multiple mechanisms may include the posterior pituitary. Diuresis and loss of edema may precede improvement in plasma protein. Salt-poor albumin intravenously is used in emergent treatment of edema; most of the administered albumin appears in the urine.

Course: In most cases the progression is towards renal failure; in lipoid nephrosis usually toward recovery if complications are prevented. Basic principles: moderate rest, sodium restriction, protein replacement, prevention of infection, urinary alkalinization. Other modes: thyroid—in some disrepute since low basal metabolic rate probably due to water logging and not tissue defect in metabolism; remissions after measles or occasionally other infections not infrequent; thus pyrogens have been used and even yellow fever vaccine. There is probably some effectiveness of ACTH, although no adequate reports have been published.

KIDNEY TUMORS—CLINICAL ASPECTS

Charles C. Higgins, M.D.

Most malignant tumors of the kidney arise on the renal parenchyma and are most frequently observed in the sixth decade. The epithelial parenchymal tumors, namely adenocarcinomas and alveolar carcinomas, are the common types in adults.

The classical triad of symptoms is hematuria, pain, and tumor. Such symptoms may also be associated with other pathologic lesions of the kidney. By the time these three symptoms are present the favorable opportunity for a surgical cure has frequently passed.

Hematuria in our series was the initial symptom in 49 per cent of the cases. The

bleeding is usually intermittent and not profuse, the blood being well mixed with the urine. When profuse bleeding is present, blood casts of the ureter may be observed.

Pain was present in 46 per cent of our cases and was the initial symptom in 28 per cent. This is a dull, aching pain in the renal area or at times, when more profuse bleeding is present, it may be a colicky pain caused by obstruction of the ureter from clots and back pressure.

A demonstrable tumor was the initial symptom in 10 to 12 per cent of the cases.

Occasionally a metastatic lesion, cachexia, or an unexplained fever may, in the course of examination, lead to the detection of a renal neoplasm. The diagnosis is established by the history, physical examination, laboratory data, and pyelography. The retrograde pyelogram reveals deformity of calices or pelvis or both.

Primary tumors of the kidney pelvis are relatively rare as compared to tumors arising in the renal parenchyma. We have observed 37. Swift-Joly collected 337 such tumors from the literature. The symptoms are hematuria, pain, and tumor.

Hematuria is the most frequent symptom and occurs in 75 to 80 per cent of cases. In 33 of our 37 cases gross hematuria was present, the duration from 1 day to 3 years. In 4 instances blood cells were detected on microscopic examination of the urinary sediment.

The next most frequent symptom is pain which occurred in 24 of the 37 cases. The pain is usually dull, boring-like, a heavy, uncomfortable feeling in the renal area. Six patients experienced renal colic due to clots.

A mass was palpable in 13 of the 37 patients. The tumor frequently involves the ureteropelvic junction thereby producing varying degrees of hydronephrosis. Loss of weight, cachexia are late manifestations of the disease. Fever was present in 11 of the 37 cases.

Papillary tumors of the renal pelvis involve the ureter or the immediate vicinity of the ureteral orifice in the bladder whether the tumor is benign or malignant. This demands a more radical surgical procedure than that necessary for squamous cell carcinoma of the kidney pelvis or primary tumors of the renal parenchyma. The diagnosis is established by the history, physical examination, microscopic examination of the urinary sediment and retrograde pyelography. The Papanicolaou examination is of considerable importance in the diagnosis of such tumors.

A nephrectomy is the treatment of choice for carcinomas of the renal parenchyma. Due to the frequent involvement of the renal vein by tumor thrombi, the renal pedicle must be ligated before manipulating the kidney. Therefore, when dealing with large tumors, the transperitoneal approach is preferred as it permits ligation of the pedicle before manipulating the kidney, thus preventing the dissemination of tumor cells into the circulation from the renal vein.

For papillary tumors of the renal pelvis (benign and malignant) a nephroureterectomy with excision of a portion of the bladder about the ureteral orifice is indicated and required. A nephrectomy suffices for the treatment of squamous cell carcinoma of the renal pelvis.

Early diagnosis is essential in the treatment of malignant tumors of the kidney. To minimize the clinical significance of hematuria is exceedingly dangerous. Blood in the urine is a symptom demanding complete urologic investigation and is not a disease for which a prescription is to be offered the patient.

PRIMARY EPITHELIAL NEOPLASMS OF THE KIDNEY

John B. Hazard, M.D.

Renal neoplasms with epithelial components may be classified as follows:

A. Benign
   1. Adenoma
   2. Papilloma

B. Malignant
   1. Embryoma (Wilms' tumor), including embryonal carcinoma and sarcoma.
   2. Renal cell carcinoma (hypernephroma).
   3. Transitional cell carcinoma.
   4. Squamous cell carcinoma.
   5. Mucinous adenocarcinoma.
   6. Tubular carcinoma.

Certain embryologic features are of interest in the derivation of some of these neoplasms. The renal 'cap' provides the genesis for renal cell carcinoma and adenoma and is formed from the metanephros. Papillomas and carcinomas of the renal pelvis and adenomas and carcinomas of the collecting tubules, arise from adult structures whose anlage is the Wolffian duct. Embryoma (Wilms' tumor) finds its origin in remaining primitive elements of the renal blastema (mesonephros).

Adenomas of the kidney are most always of renal cell origin, only rarely being derived from the collecting tubules. They are of two types: (1) Small adenoma, often multiple and nonencapsulate. (2) Large adenoma, solitary and with well-defined capsule. The small adenomas may be bilateral and may bear a genetic relationship to renal cell carcinoma. They vary in size from a few millimeters to 2 cm., the larger forms rare, and all incidental findings in the pathologic examination of the kidney. The majority are papillary, wholly or in part. The large adenomas may measure 10 cm. or more in size and are of much less common occurrence. They may be papillary or nonpapillary.

Papillomas are of transitional cell type and may be multiple in the renal pelvis. Similar tumors are often concomitant in the ureter and bladder. Transitional cell carcinoma and squamous cell carcinoma may find origin in these tumors.

Carcinomas of the kidney are divided into two general groups, one of renal cell origin, the other of transitional cell derivation. The renal cell carcinomas arise in the cortex of the kidney, are over 1.5 cm. in diameter and grossly may be circumscribed or infiltrating. They are yellowish, often with areas of hemorrhage and with zones of degeneration evidenced by necrosis and fibrosis. Histologically, the cells usually have well defined margins and clear cytoplasms, the so-called clear cell variant or hypernephroma. These neoplasms, however, are rarely of pure type, and in addition to the characteristics mentioned there are cells of smaller size with granular pink staining cytoplasm forming lumina or tubular structures, spindle cell forms, at times simulating sarcoma, and areas of papillary architecture. The pure types are rare; they may be found as the clear cell carcinoma, granular cell carcinoma, or tubular carcinoma of the kidney. The renal cell carcinomas often invade the renal pelvis and extend into the veins, at times invading the main renal vein or even growing into and filling the inferior vena cava. Occasionally the renal capsule is penetrated and the neoplasm extends into the perirenal fat tissue. Distant metastasis occurs most commonly to bones, and lungs, but other sites may be secondarily involved; several instances of thyroid involvement have been recorded. Solitary metastases may occur and there have been reports of long survival following removal of the metastatic tumor and the primary neoplasm of the

kidney. Transitional cell carcinomas are derived from the epithelium of the renal pelvis and may occur as a neoplasm formed of tissue resembling the usual epithelial lining of the pelvis, or as squamous cell carcinoma. As to gross appearance, they may be villous or solid. They may grow superficially or show definite infiltrating properties. They are generally of gray or gray-white color. Microscopically, the transitional cell type is most common and a papillary configuration usual, although at times they may show a non-papillary arrangement. They invade veins less frequently than renal cell carcinoma, but have a greater tendency to extend into the tissues about the renal pelvis. The ureter and bladder may show concomitant occurrence of transitional cell carcinoma which may be regarded as either implant or as tumors of multicentric derivation. The neoplasms metastasize to regional lymph nodes and distant organs. Squamous cell carcinoma of the renal pelvis has an especially poor prognosis.

Embryoma is commonly known as Wilms' tumor and belongs to the group of mixed neoplasms. In gross appearance it is of large size, circumscribed, often encapsulate and gray to yellowish in color. Microscopically, it is of mixed structure, growing as embryonal carcinoma, as embryonal sarcoma, or at times as an undifferentiated cell type defying classification. Primitive elements simulating embryonic glomerular structures are found in typical specimens. The mesenchymal elements may at times predominate to form a firm, tough tumor mass which, because of its encapsulate appearance, may be grossly mistaken for a fibroma. However, if sufficient sections are taken, embryonal elements are always found to be present. These tumors metastasize regionally and often show extensive distant metastases.

There are certain morphologic features which bear a relation to the prognosis of primary carcinoma of the kidney. Among those indicative of a poor prognosis are: direct extension to perirenal tissues; microscopic dedifferentiation; growth activity as evidenced by frequency of mitoses; angio-invasion, especially by transitional cell carcinoma and the more dedifferentiated forms of renal cell carcinoma.

ELECTROLYTE AND CHEMICAL FEATURES OF UREMIA

A. C. Corcoran, M.D.

The chemical features of uremia can be classed as (1) those due to retention of substances in blood, (2) those due to uncontrolled excretion of substances in urine, and (3) reactive changes.

In uremia due to acute and total loss of renal function, e.g. in lower nephron nephrosis, the most important changes are due to retention. Potassium intoxication is a common immediate cause of death. Acidosis, anemia, and hypocalcemia are not major features.

In contrast in slowly developing uremia, the clinical syndrome is marked by a preponderance of evidences of central nervous disturbance. These have been ascribed to a hypothetical "uremic toxin," the activity of which is somehow associated with protein catabolism. Azotemia can reach tremendous levels. Acidosis, due in part to failure of renal ammonia-formation and in part to retention of phosphate and sulfate, is an important complication, and anemia is often severe. The reactive changes of parathyroid hyperplasia due to phosphate retention may be of both diagnostic and clinical significance. Inability to retain sodium, water, and even potassium may also precipitate remediable complications. Interestingly, a similar inability to retain electrolytes occurs during the first days of recovery from acute anuria.

NEPHROSCLEROSIS AND HYPERTENSIVE RENAL DISEASE

Robert D. Taylor, M.D.

The nephrosclerosis of hypertensive disease differs from nephrosclerosis of old age only in the period of life at which it becomes apparent and the rate with which it progresses. The changes consist of hyalinization of the media and proliferation of the intima so that the vascular lumen is greatly narrowed and eventually obliterated. The natural consequence is impaired function and death of the tissues nourished by the diseased vasculature.

In the case of essential hypertension this process is slowly progressive and only 2 to 4 per cent of such patients die of renal failure. Cardiac or cerebral diseases are more common causes of death. In the malignant phase the sclerotic process is replaced by a much more fulminating process of necrosis. There is some evidence that this is due to sudden and sustained elevation of arterial pressure, while some observers feel it is the result of a specific necrotizing agent elaborated by the kidney. Be that as it may, the end result is necrotizing arteriolar inflammation, and well over 75 per cent of patients with malignant hypertension die of renal failure.

The laboratory and clinical signs of the renal disease of hypertension are characteristic. Because of arteriolar sclerosis and resulting decreased perfusion, tubular function is impaired relatively earlier than glomerular function which is maintained at or above normal by increased filtration pressure resulting from hypertension and increased arteriolar resistance to the flow of blood leaving the glomeruli. Hence, the ability to concentrate urine will be decreased while the urea clearance may be comparatively normal. Thus, one of the early signs of hypertensive renal disease is nocturia.

The urinary sediment is not greatly different from the normal in essential hypertension and proteinuria may amount to less than 0.4 Gm. per 24 hours. In the malignant phase of the disease there is hematuria, often gross, and proteinuria greater than 0.4 Gm. per 24 hours. Filtration rate falls rapidly and azotemia soon appears.

DERMATOLOGIC PROBLEMS ENCOUNTERED IN MANAGEMENT OF URINARY TRACT DISORDERS

Earl W. Netherton, M.D.

Pruritus commonly accompanies uremia regardless whether this has developed from nephritis, prostatic hypertrophy, or cardiorenal disease. Pallor and discoloration of the skin may result from edema of the tissues in nephrosis or the nephrotic stage of glomerulonephritis. Sallowness and pallor are often seen in the terminal stage of glomerulonephritis. Hemosiderin may be deposited on the skin as a result of purpura which may be associated with several urinary tract disorders. Urea frost may be seen on the skin in terminal stages of uremia and is best observed in negroes.

Numerous other manifestations on the skin are often associated with uremia including xeroderma, eczematoid dermatitis, miliaria crystallina or sudamen, and acne vulgaris and rosacea, and pyoderma. Impetigo, furunculosis, and other infections are at times aggravated by uremia. Keratodermia blennorrhagicum is characterized by urethritis, arthritis, and an eruption consisting of vesicles, vesiculopustular and adherent waxy, semitransparent, thick, horny crust. The areas of predilection are the hands, feet and distal portions of the extremities. It is caused by the gonococcus. Reiter's disease, which is a condition of unknown origin, is characterized by conjunctivitis, arthritis, and urethritis and is at times associated with lesions simulating those of keratodermia blennorrhagicum. In paroxysmal hemoglobinuria urticarial and vesicular

lesions on the skin may develop. Porphyruria, which is a rare constitutional anomaly, is associated with sensitivity of the skin to sunshine. Exposure to the sun may produce vesicular and bullous eruptions in this disease. Perhaps the most common dermatologic manifestation associated with urinary tract disorders are the drug eruptions resulting from treatment of the underlying urologic disorder. Eruptions resembling purpura, erythema multiforme, urticaria, eczematoid dermatitis, scarlatina or measles are not uncommon results of drug therapy.

THE HEART AND ELECTROCARDIOGRAM IN UREMIA

William L. Proudfit, M.D.

The characteristic electrocardiographic alterations in uremia are due to disturbance in the electrolyte balance and pericarditis.

Hypocalcemia is frequent in uremia. It is due to the retention of phosphates secondary to kidney disease. The characteristic electrocardiographic finding in hypocalcemia is an unusual prolongation of the Q-T interval. The form of the T-waves is normal, but there is an unusually long, flat RS-T segment.

Hypopotassemia may occur in uremic patients. The Q-T interval is prolonged as in hypocalcemia, but the configuration of the RS-T segments and the T-waves is characteristic. In contrast to hypocalcemia, the RS-T segment is of normal duration, and the Q-T interval is prolonged due to increased duration of the T-waves. Prominent U-waves are frequent in hypopotassemia, and at times the U-waves appear to be incorporated with the T-waves, causing further apparent prolongation of the Q-T interval. These changes disappear entirely after the administration of potassium salts by mouth or parenterally.

Hyperpotassemia may develop, either as a result of increased tissue breakdown with retention of the potassium liberated or retention of potassium salts given by mouth. The heart sounds may be muffled. The earliest electrocardiographic change secondary to hyperpotassemia is an increase in the height of the T-wave with a peaking of the crest of the wave. Subsequently the QRS complex may become wider, and finally auricular asystole may appear. The heart stops in diastole.

The clinical and electrocardiographic changes of fibrinous pericarditis in uremic patients differ in no way from those in nonuremic subjects. In some cases of uremic pericarditis the electrocardiographic changes may not be striking, or may be absent.

Combinations of these disturbances may occur in uremia. The presence of changes indicative of both hypocalcemia and hyperpotassemia is highly suggestive of uremia.

APPOINTMENTS

Dr. Fred R. Tingwald has been made a member of the staff in the Department of Otolaryngology. Dr. Tingwald was graduated from the State University of Iowa in 1937 and received the M.D. degree from that institution in 1938. Following a two year internship, he served a residency in pathology for one year at the Youngstown (Ohio) Hospital Association. Dr. Tingwald was with the U. S. Army from 1941 to 1945. He then returned to the University Hospital, Iowa City, where he spent three years as resident in otolaryngology. On completion of this residency he was made assistant in otolaryngology at the State University of Iowa College of Medicine. Dr. Tingwald was certified by the American Board of Otolaryngology in 1948.

On March 20, Dr. Willem J. Kolff joined the assistant staff in the Research Division. Dr. Kolff studied at the University of Leyden and was assistant in the Department of Pathology at that university. On completing his medical studies in 1938, he was assistant in the Department of Internal Medicine at the University of Groningen and in 1941 became head of the medical department of a small municipal hospital in Kampen, Holland. Dr. Kolff received his doctor's degree at the University of Groningen in 1946. During 1947 he made a lecture tour of four months in the United States, received the Amory Award in Boston presented by the American Academy of Arts and Sciences, and was made an honorary fellow of the American Medical Association. In 1947 Dr. Kolff's monograph "New Ways of Treating Uremia" was published by J. and A. Churchill, London.

Cleveland Clinic Quarterly

THE TREATMENT OF PEPTIC ULCER

Present Status, Including Vagotomy

E. N. COLLINS, M.D.
Department of Gastroenterology

"RECENT measures advocated for the treatment of peptic ulcer range from pituitary 'snuff' to fresh cabbage juice! To these can be added mucin, protein hydrolysates, amino acids, resins, certain detergents and what have you." This quotation is from an article by George B. Eusterman in the 1949 Year Book of Medicine. The number of treatments for peptic ulcer are indeed unlimited.

Although each patient presents an individual problem, all clinicians are agreed that first attention should be given to the patient's general health, including his hygienic needs such as living habits, physical and mental rest, and proper nutrition.

The methods employed in treating peptic ulcer at Cleveland Clinic depend primarily upon the location of the ulcer. Analysis of our records show that 85 per cent of patients having duodenal ulcers make satisfactory progress on medical management alone. Most of the other 15 per cent, having intractable duodenal ulcers and/or complications, have been benefited by bilateral vagus resections plus gastroenterostomy. Gastric resection is being employed in most patients having gastric ulcer.

This discussion is divided into three parts: first, gastric ulcer and the complications of peptic ulcer in general; second, the medical management in patients having uncomplicated duodenal ulcers, and finally, a 2 year follow-up study of our first 100 consecutive patients with complicated duodenal ulcers who have had bilateral vagotomies plus gastroenterostomy or pyloroplasty. During the past 4 years 495 patients have had bilateral vagotomies.

Part I

Gastric Ulcer

When an ulcerating carcinoma of the stomach is demonstrated by roentgen and/or gastroscopic examination, gastric resection obviously is indicated. However, the problem of whether or not the gastric ulcer is benign or malignant is frequently encountered. When it is in the distal third of the stomach we believe that gastric resection is indicated, even though the ulcer may prove to be benign. Malignant lesions are most common in this area.

Unlike duodenal ulcer, gastric resection for a benign gastric ulcer is rarely, if ever, followed by the formation of a jejunal ulcer. The results are usually excellent.

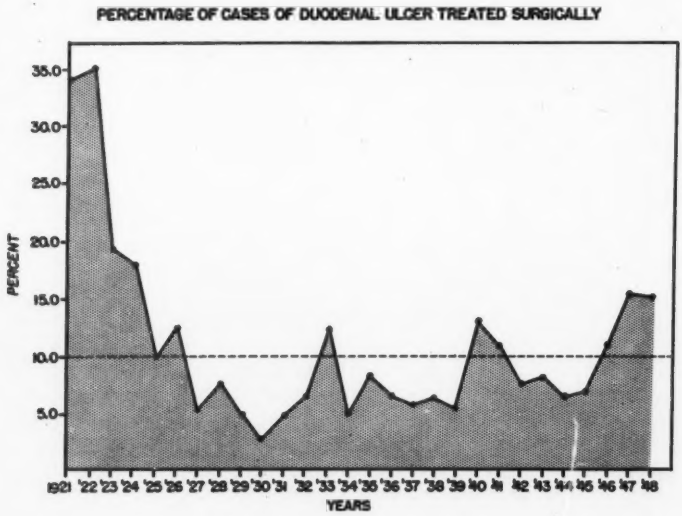
When the ulcer is on the lesser curvature in the pars media of the stomach and the patient presents a history of attacks characteristic of benign ulcer which have recurred for years, and when the roentgenologist and gastroscopist agree that the ulcer is benign, we may advise strict medical management provided re-check examinations are made in 1 month.

We have seen a number of instances where the roentgen and gastroscopic findings were questionable, and where at operation the surgeon believed the gastric ulcer benign as did the pathologist. Frozen sections disclosed no evidence of a malignant process but paraffin sections following gastric resection revealed a malignant disease. We re-emphasize our conviction that, in most instances, gastric resection is the treatment of choice for gastric ulcer.

Dr. George Crile, Jr. observes that, when dealing with a high gastric ulcer a centimeter or two from the esophagus, a more conservative procedure than total gastrectomy should be considered, such as excision of the ulcer coupled with gastroenterostomy, or gastroenterostomy with vagotomy. It is assumed that no cancer cells are found in the frozen biopsy specimen.

Duodenal Ulcer

The accompanying graph shows trends we have experienced in the surgical treatment of duodenal ulcer. It will be observed that in 1921, 35 per cent of patients had operations, i. e. gastroenterostomies. This period was followed by one of gastric resections (at that time the curve was as low as 5 per cent), and now, with the advent of bilateral vagotomy plus gastroenterostomy or pyloroplasty, the curve has risen to 15 per cent. It should be emphasized that surgery is employed for duodenal ulcer only when complications are present



such as acute perforation, two or more massive hemorrhages, or pyloric obstruction due to true cicatricial narrowing. It is indicated also for patients who continue to have intractable symptoms while on strict medical management.

Acute Perforation

Regardless of its location an acute perforation should, of course, have simple closure as soon as possible. It is a lifesaving procedure. A gastroenterostomy is combined with simple closure only if the ulcer is in the pyloric canal or associated with pyloric obstruction.

In recent years, since antibiotics and sulfonamides have become available, we occasionally see a patient on whom surgery is not performed immediately. Sometimes a patient is not observed until 24 hours or more following a small perforation by which time a "walling off process" has occurred. Constant Wangensteen suction, the use of 100,000 units of penicillin every 2 hours with or without intravenous sodium sulfadiazine and with parenteral fluid therapy, has resulted in postponement of surgery until an elective type of operation, such as vagotomy and gastroenterostomy, could be performed. Colonel Seeley and associates[1] at Fort Sam Houston, Texas, treated 34 cases of perforated duodenal ulcers in a similar manner without operations and without a single death.

In most cases we still believe prompt closure of the perforation to be the preferred treatment.

Massive Hemorrhage

Our present treatment of massive hemorrhage is influenced by the age of the patient, evidence of definite arteriosclerosis, and the immediate response to medical management. If operation during the massive hemorrhage is indicated, it should be performed preferably during the first 48 hours, in combination with a continuous "drip method" of blood transfusions. Although we believe this complication to be primarily a medical problem at the time of the hemorrhage, a surgeon familiar with all the details should be in constant attendance, prepared to operate at a moment's notice.

In this issue of the *Cleveland Clinic Quarterly* Dr. Stanley O. Hoerr has given our criteria for emergency operation. "The crux of the matter is the rapidity of the bleeding." Each patient presents an individual problem. It is commonly stated that young patients rarely require surgery at the time of active bleeding. However we have found that occasionally a patient below the age of 50 may continue to bleed while on medical management, while a patient of 70 years may have a sudden cessation of hemorrhage.

Medical management includes immediate sedation, such as sodium phenobarbital, gr. 1 or 2, and atropine sulfate, gr. 1/100, given hypodermically and repeated every 2 or 4 hours, in quantity sufficient to allay apprehension and to keep the patient drowsy. Morphine may increase the tendency to nausea and vomiting. Feedings of a bland type, including ground meat, are

given immediately at 2 hour intervals, and antacids are given between feedings; the antacids are repeated during the night hours.

Dr. Hoerr has summarized our convictions relative to blood transfusions. Although blood counts, including hematocrit readings, are made daily in an attempt to determine the *rapidity of bleeding*, most reliance is placed on efficient nursing care, the general condition of the patient, frequent determinations of the quality and rapidity of the pulse, and blood pressure determinations. Due to factors of dehydration and hemoconcentration, the blood counts may rise during active bleeding and fall when dehydration has been corrected and active bleeding has ceased.

Daily blood urea determinations have proved significant from the standpoint of prognosis. A high initial reading is associated with shock, with diminished flow of blood through the kidneys, as well as absorption of blood from the intestinal tract. If the blood urea level returns to normal in 2 or 3 days the patient obviously is not in immediate danger; if it continues to rise surgical intervention is strongly indicated. The color of the stools and tests for occult blood are observed daily but may not become negative until 10 days following the cessation of bleeding; thus stool examinations are valueless in determining immediate treatment, although reassuring when negative.

Surgeons prefer to operate when the massive hemorrhage has subsided, the lesion is localized, and the patient is in good condition. If the patient gives a history of two or more massive hemorrhages, we believe surgery should be employed regardless of age, and preferably when the bleeding has ceased and the patient is completely rehabilitated.

Pyloric Obstruction

Brilliant results follow the use of gastroenterostomy alone when the patient is 70 years old and the obstruction is due to a cicatrix of a healed ulcer. However, a patient 30 years of age, observed at the time of his first pyloric obstruction when undergoing considerable dilatation of the stomach due to an active duodenal ulcer, may overcome the symptoms and signs within a few days on medical management. In this instance the obstruction may be due to spasm or inflammatory edema. In the event of recurrent obstruction, surgery is unquestionably indicated.

Criteria which establish the diagnosis of true pyloric stenosis due to cicatricial narrowing should include observation on adequate medical management during a period of at least 5 days.[2] The same method is followed in preparing the patient for surgical treatment, so that no time is lost. Decompression of the stomach by daily gastric aspirations and continuous suction, at least during the night hours, are extremely important. Utilization of a new plastic tube has proved a more comfortable procedure than the older Levine rubber tubes. It is necessary to obtain an accurate record of the fluid intake and output, as well as to re-establish normal chemical balance.

We find that the determinations of the 24 hour urinary excretion of chlorides are particularly important.[3] The urinary chloride excretion is a simple

procedure and is more significant than the blood chloride determination. Haden has observed that the plasma chloride content is preserved at the expense of the tissue chloride, so that the amount of chloride in the blood may be normal when the tissue chlorides are depleted. The purpose of parenteral fluid therapy is to maintain a daily urinary output of 1500 cc. with an excretion of at least 5 Gm. of sodium chloride.

Foods which, in our experience, pass through the pylorus most easily are: strained cereals with sugar and cream, plain malted milk, chocolate malted milk, eggnog (nonalcoholic), plain ice cream, junket, plain gelatins with cream, strained cream soups, cocoa made with half milk and half cream, coffee with sugar and cream from which the caffeine has been removed.

Feedings from this selection are given every 2 hours throughout the day, the last at 6 p.m. Additions are made to the diet as rapidly as tolerated. Parenteral vitamins are given as indicated by clinical evidence of deficiency and the history of dietary inadequacy. Parenteral antispasmodics are prescribed similar to those given to patients with massive hemorrhage.

Since these patients commonly have alkalosis when first observed, the preferred antacid is aluminum hydroxide gel combined with magnesium trisilicate. The antacid is given every 2 hours, alternating with feedings except at the time when gastric suction is being employed. In none of our patients has there been a disturbance of the acid base or urinary complications attributable to this preparation.

If the obstruction is relieved within a period of 5 days, and medical management is continued, treatment is simplified and the ambulatory management for uncomplicated ulcer is instituted.

Part II

Medical Management of Uncomplicated Duodenal Ulcer

As previously mentioned, at least 85 per cent of our patients having duodenal ulcers make satisfactory progress on medical management. If this is prescribed adequately early in the course of the disease, and the patient cooperates, few complications occur.

Since the cause of peptic ulcer is unknown, measures have been used in its treatment based on the hygienic needs of the patient. The work of B. W. Sippy, published in 1915, is familiar to all clinicians. Extensive experimental work since that time, summarized by Walter L. Palmer,[4] has confirmed the value of antacid therapy.

Approximately 13 years ago we observed a number of patients with peptic ulcers who also had renal calculi or other renal complications. As the urologists wished to maintain an acid reaction in the urine, aluminum hydroxide gel was substituted in these cases for the usual Sippy powders.[5] These patients made satisfactory progress, even though the number of interval feedings and doses of antacid per day were reduced. Since that time aluminum hydroxide in combination with magnesium trisilicate or other nonabsorbable antacids have been used routinely, and the results of this therapy have proved as satis-

factory as those obtained formerly with the more rigid original Sippy treatment.

Evaluation of any treatment is difficult in a disease of unknown cause subject to spontaneous remission. However, as shown on the graph, the trends in surgical treatment of duodenal ulcer did not change when nonabsorbable antacids were substituted for the usual Sippy powders.

In treating these ulcers we attempt to effect more than the immediate relief of the symptoms. Satisfactory response to medical treatment is evidenced when ulcer craters disappear by progress roentgen examination as well as by gastroscopy in patients having gastric or anastomotic ulcers. These examinations are regulated according to the severity of the initial problem; even though they appear favorable, medical management is continued. However, the patient is advised to have further check-up examinations during the first year's treatment and at least annually during the next several years.

It is now generally agreed that adequate antacid therapy does not require complete neutralization of gastric acidity. The purpose is to keep the level of free acidity low enough to prevent activation of pepsinogen, the proteolytic neutralization point emphasized by Hollander.[6] Eyerly and Breuhaus[7] demonstrated by repeated electrometer readings, checked by repeated examinations of aspirated material over a 3 hour test period, that boiled egg white failed to digest when the stomach contents were maintained at a pH of 3.5 or higher.

James Flexner and his associates,[8] using a method for the continuous recording of gastric pH in situ (which included a pumping system to maintain circulation of the mixture around the glass electrode), studied the efficacy of numerous antacids and found that aluminum hydroxide gel had a prolonged antacid effect when prescribed in suitable dosage. The Komarovs[9] and Schriffrin and Komarov[10] demonstrated the precipitation and inactivation of pepsin in vitro and in vivo in dogs by the alumina gels without excessive reduction of acidity.

The intensity of our present therapy naturally varies with the severity of the disease and with the patient. Although details vary, standard medical management for uncomplicated duodenal ulcer during the first 6 weeks includes the use of a "smooth diet" and a glassful of milk or food every 2 hours while awake.

Diet

The diet has been liberalized in many instances. Vegetables and fruit are not pureed but in all instances the patient is advised to avoid seeds, skins and coarse fibers as long as he lives. While most patients with peptic ulcer like milk the most important feature is not how much they consume per day, but how often.

During the first week all foods except vegetables and fruit are allowed. Cooked vegetables and fruits are added during the second week. During the third week, and thereafter, the patient is on a well-balanced diet, including raw vegetables and fruits and juices.

Antacids

We have tested many antacids, detergents, mucin-combinations and other preparations by doing hourly aspirations and titrations of the patient during several 24 hour periods; in many instances with each substance. Beckman pH determinations using tenth normal hydrochloric acid with various "anti-ulcer" substances also have been made in vitro.

Nonabsorbable antacids, chiefly aluminum hydroxide, have been used in the Clinic during the past 13 years. In addition to their antacid property, aluminum hydroxide preparations have astringent, adsorptive, bactericidal, and demulcent properties, and they inactivate pepsin without excessive reduction of gastric acidity. Also, they can be prescribed without danger to the acid-base balance of the patient or of urinary complications. Formerly, milk of magnesia was added to prevent the constipating effect of aluminum hydroxide, but this is rarely needed now because we use aluminum hydroxide with magnesium trisilicate preparations.

The liquid forms are preferable and are used while the patient is in the hospital or around home. The dosage varies according to the gastric acidity but averages 2 teaspoonfuls (stirred in a third of a glass of water) every 2 hours during waking hours throughout the first 6 weeks of treatment, and 1 ounce on retiring. If the patient has had night pain he is advised to set his alarm clock and take 1 ounce at midnight and at 3 a.m. during the first week. In other words, during the first stage of the treatment the patient takes milk or food one hour and antacid the next, thereby alternating the two every waking hour. If he continues to work, tablets are substituted for the liquid when away from home for the sake of convenience. Antispasmodics and/or mild sedatives are used during the first 3 weeks' treatment.

We call the above treatment "minimal therapy." If the patient does not experience immediate and complete relief of symptoms, we conclude that the diagnosis was wrong or that a "surgical ulcer" exists. However, even though the patient has had complete relief of symptoms, we always advise progress roentgen examinations (and gastroscopic examination if the patient has a gastric ulcer), at the end of 6 weeks. Management is adjusted according to all details but he is advised to take milk or food at least once between meals and an antacid at least 4 times daily as long as he lives, as a means of preventing recurrence. Should the symptoms recur he must at once revert to the original schedule.

Roentgen Therapy

Palmer and his associates[11] at the University of Chicago have reported their results in 800 cases of peptic ulcer studied from 1936 to 1947. The optimum depth dose was found to vary from 1600 to 2500 r in 12 days. Ulcer pain disappeared and healing occurred uniformly during periods of achlorhydria. However, the duration of achlorhydria was unpredictable. It varied from a few days to as long as 8 years, the average being several months.

We have used radiation therapy in rare instances, particularly in patients with intractable symptoms who refused operation. The immediate results were

usually favorable but invariably the patients developed recurrent ulcers within a few months.

Protein Hydrolysates

Protein hydrolysates have been used in the treatment of peptic ulcer since 1942, when Levy and Siler[12] reported a noticeable buffering action on gastric acidity. For several months we substituted various forms of protein hydrolysates for our usual antacid therapy but the patients objected to the taste of the medicine as well as to the cost. Inasmuch as progress x-ray examinations were also unfavorable, its use was abandoned.

When, in 1945, Co Tui and his associates[13] at New York University reported favorable results in a small group of patients given protein hydrolysate and dextrimaltose, we tried this form of treatment but were again disappointed in the results.

Woldman and his associates,[14] working at St. Luke's Hospital in Cleveland, found there was a sharp rise in the free acidity in the stomach after the period of neutralization with protein hydrolysate. Multiple doses of 25 Gm. every hour ceased to neutralize free hydrochloric acid in the stomach; in fact the continuous drip of a 10 per cent solution failed to neutralize the acid. Although the ulcer pain continued for from 24 to 72 hours at the beginning of this treatment, it disappeared immediately in the patients receiving aluminum hydroxide gel. Recurrence of the ulcer within a short period after treatment was more common during treatment with protein hydrolysate, and this included such complications as hemorrhage and perforation. It was concluded that protein hydrolysate is valuable as a food, but has little value as a therapeutic agent in peptic ulcer.

Enterogastrone

Enterogastrone, an extract of hog-intestinal mucosa, depresses the secretion of acid by the gastric glands when administered intravenously to dogs. According to Ivy and associates[15] at the University of Illinois, enterogastrone extracts prevent postoperative jejunal ulceration in a high percentage of dogs with the Mann-Williamson operation, in 98 per cent of which ulcer ordinarily develops. They note as remarkable the fact that the anti-ulcer effect extends well beyond the period of administration of the extract; in most instances at least several years.

In the human subject intramuscular injections are given 6 times a week for 1 year. The recorded results to date are not better than antacid therapy. The cost of treatment and the inconvenience to the patient are important items. We have had no clinical experience with enterogastrone.

Banthine

Since January 1, 1950, we have used Banthine* (a drug with anticholinergic effects) in 20 patients having complicated duodenal ulcer. The initial response

*Generously supplied by the Searle Company.

to the use of this drug has been favorable. Several physicians requested the use of Banthine before resorting to vagotomy with gastroenterostomy, and they have obtained satisfactory results without surgery. A long-term "follow-up" study will be required before evaluating this or any other form of treatment for peptic ulcer.[16,17]

Part III

Bilateral Vagotomy

The extensive work pertaining to this subject by Lester Dragstedt and his associates is well known. Members of our medical division have welcomed bilateral vagotomy in patients having intractable pain or complicated duodenal ulcers because they have witnessed the immediate relief of pain; the morbidity, as well as the mortality rate, has been lower in these patients than in those having gastroenterostomies or gastric resections alone. Many surgeons now agree that bilateral vagotomy is the procedure of choice in patients having jejunal ulcers following gastric resections. Dr. Dragstedt has reiterated, "Since we are agreed that bilateral vagotomy is the treatment of choice for jejunal ulcer, why does not this procedure apply to other simpler forms of peptic ulcer?"

Since January, 1946, 495 bilateral vagotomies have been performed at the Clinic. Vagotomy has passed through several stages in our experience. The transthoracic approach was used first. Thereafter the transabdominal approach without drainage was employed unless there was obvious pyloric stenosis. For a time gastric ulcers were treated by this procedure.

At the present time, as stated previously, gastric resection is the surgical treatment of choice in gastric ulcer. Vagotomy is not done at the time of a massive hemorrhage for any form of peptic ulcer. Vagotomy plus gastroenterostomy or pyloroplasty is the treatment of choice for complicated duodenal ulcer. The mortality rate for vagotomy with gastroenterostomy has been under 1 per cent.

Transabdominal vagotomies with or without revisions of the stoma in 31 patients with proved cases of marginal ulcers have given the following results: 21 excellent, 5 satisfactory, 2 improved, and 3 failures.

Results of 2 year follow-up studies of the first 100 patients having bilateral vagotomies plus gastroenterostomies or pyloroplasties for complicated duodenal ulcers follow:

Bilateral vagotomy plus gastroenterostomy . . 73 patients
Bilateral vagotomy plus pyloroplasty . . . . . 27 patients
(Operations performed by the late Dr. T. E. Jones and Dr. George Crile, Jr.)

Complications prior to operation:

Pyloric obstructions	24
Massive hemorrhages	21
multiple	9
Acute perforations	10
multiple	2

Twenty of the 24 patients having pyloric obstructions had 50 to 100 per cent gastric retention in 6 hours, as evidenced by roentgen examination. More than half of the patients in this series had intractable pain, including night pain, and medical management was ineffective.

The sex and age distribution and the duration of symptoms follow:

100 consecutive patients having complicated duodenal ulcers

Sex . . . . . 85 men 15 women

Age . . . . . Average—47 years

Duration of ulcer symptoms (prior to vagotomy)—average 12.6 years

Results of Follow-up Studies

Results to date are known in 97 of the first 100 consecutive patients. One patient died in the hospital and 1 died 6 months after operation of an unrelated disease. We were unable to trace 2 patients. Another patient had obtained an excellent result at the end of 9 months, but we have not seen him recently. Therefore, the present follow-up study concerns 95 patients who have been followed for an average of 2 years.

Insulin tolerance tests, unless positive, have not proved reliable in determining the completeness of the vagotomies in this investigation because of regurgitation of duodenal contents. Drainage studies have proved important, and postoperative roentgen examinations equally so.

In an attempt to appraise the results in 95 patients having follow-up studies over a period of 2 years, the following criteria were used:

Excellent . . . 100 per cent normal health from gastrointestinal standpoint.

Satisfactory . . No ulcer distress; gastrointestinal symptoms so mild that they do not interfere with work; no special diet or medication used.

Improved . . . No ulcer distress; fewer gastrointestinal symptoms than before operation, but diet and/or medication have been used to control symptoms.

Failure . . . . Persistence of ulcer-like distress or development of other gastrointestinal symptoms sufficiently severe to constitute disability.

	Excellent	Satisfactory	Improved	Failure
Cases	62	20	10	3

Excellent plus satisfactory—86 per cent. (Patients with complicated duodenal ulcer).

Three of the 95 patients were considered to be in the failure group. One patient developed a jejunal ulcer. At a subsequent operation he was found to have had an incomplete vagotomy. The other 2 patients continue to have intermittent ulcer-like distress but progress roentgen examinations have revealed no evidence of ulcer craters. Motility studies of these patients were normal; stomas functioned normally. One patient, a retired physician, has symptoms referable to many parts of the body, particularly the cardiovascular

system. The other patient is a 28-year-old registered nurse who had epigastric burning at times, as well as intermittent diarrhea not exceeding 4 stools in any 24 hour period. Although her roentgen examination demonstrated an excellent result from the operation, she has used antacids at times and is therefore considered a failure.

The patients who are placed in the excellent and satisfactory groups are following no special diet, taking no medicine, and have no significant symptoms. This is in contrast to the patients having partial gastrectomies or gastroenterostomies without vagotomy, where intensive postoperative medical management, including the use of antacids, is usually advised. It will be noted that 92 patients included in the first three categories are free of ulcer distress and are in much better health than before operation. Only 3 of the 95 are classified as failures.

Comment

The present report deals with the first 100 consecutive patients having bilateral vagotomies combined with gastroenterostomies or pyloroplasties for complicated duodenal ulcers. Of these we were able to follow 95 over an average period of 2 years.

Renshaw and Beck[18] reviewed 25 years' experience of our staff with conventional surgery, i. e. gastric resection or gastroenterostomy alone. The greatest percentage of recurrences occurred within the first year after operation.

The patients in the group reported here have obtained better results than comparable series of patients having conventional surgery followed over a similar period of time. The mortality rate was 1 per cent. One patient developed a jejunal ulcer with obstruction. At a subsequent operation he was found to have had an incomplete vagotomy. Otherwise no patient in this series has developed roentgen evidence of recurrent ulcer, and no patient has had a recurrence of obstruction, hemorrhage, or perforation.

At the present time, when elective surgery is indicated for complicated duodenal ulcer, our group favors bilateral vagotomy plus gastroenterostomy or pyloroplasty.

The final evaluation of any form of treatment for peptic ulcer must, of course, be based on years of experience, always bearing in mind that this disease is characterized by spontaneous remissions.

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MASSIVE UPPER GASTROINTESTINAL HEMORRHAGE

The Selection of Patients for Emergency Operation

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SUDDEN massive hemorrhage from the upper gastrointestinal tract is an unwelcome emergency. It is no longer sound practice to treat every patient with this condition by conservative measures, and the physician therefore is taxed with a delicate question: Which patient will require an emergency operation to save his life? The problem is rendered no less difficult by the fact that it is only the occasional patient—less than one in ten—in whom such an operation will be necessary. The physician (and the term is used to include family physician, internist, gastroenterologist or surgeon) should adopt the view that emergency surgery is to be performed only upon that patient who he believes may die without operation.

How can this occasional patient be selected for emergency operation? The crux of the matter is the **rapidity of the bleeding**. Other factors such as the duration of the hemorrhage, the age of the patient and the number of previous hemorrhages, are of secondary importance. The reasoning behind this view is that in slow hemorrhage, no matter how persistent, the physician can keep abreast of the bleeding with blood transfusion, and sudden circulatory collapse with death from exsanguination is unlikely. Occasionally a slow but persistent bleeder will require surgery while the bleeding is in progress (Case 3) but a more leisurely decision is then possible. The most reliable guide to the rapidity of the hemorrhage is the state of the circulation; in rapid hemorrhage, peripheral vascular collapse is present or impending.

It is rarely possible to decide within the first few hours of observation whether or not an emergency operation will be necessary. Many patients will experience weakness or syncope at the onset of a moderate or even a mild hemorrhage, often coincident with the effort of vomiting or moving the bowels. Recovery is usually prompt, and this initial syncope is not evidence in itself of a massive hemorrhage. Other patients will be in a state of clinical shock upon arrival at the hospital, but a single transfusion of 500 cc. whole blood is sufficient to bring the blood pressure back to normal and slow the pulse rate. The patient may remain in a stable circulatory state from then on. An occasional patient of this type may need as much as 1000 to 1500 cc. of blood within the first few hours before his circulation is stabilized (Case 1); if more than this is required one must fear that rapid hemorrhage is continuing and may prove fatal without operative intervention (Case 2).

Once the initial shock has been successfully combated, the physician must be prepared to play a waiting game. Nine out of 10 patients will either cease

bleeding promptly, or will bleed at rates which are compensated easily by a reasonable number of blood transfusions. We have found it useful to set a limit to the number of transfusions which the patient should require on a conservative regime. We have set this limit arbitrarily at 500 cc. of blood for every 8 hour period, day and night. If the patient is losing blood so rapidly that transfusions at this rate do not make up the loss, operative intervention should be contemplated.

How may one determine the rate of bleeding in the patient who is under observation and is receiving conservative therapy? Operation is to be considered for dangerously rapid bleeding under the following circumstances:

1. **Recurrence of syncope or shock.** Patients in whom this occurs are almost invariably bleeding from a single large vessel which temporarily closes off only to start again at an alarming rate. There may be a latent period of several days between hemorrhages, and it is not unusual for the untreated patient to have several such episodes. Such patients are in a precarious state and operative intervention is advisable barring special contraindications.

2. **A drop in systolic blood pressure or rise in pulse rate, especially if sudden.** Although less dramatic than syncope or shock the meaning is the same, and it usually presages recurrence or persistence of rapid bleeding. The blood pressure and pulse rate should be determined frequently at intervals varying from every 15 minutes to every 2 hours, depending on the circumstances, in the patient who is under observation for a serious hemorrhage. If instability of the circulation is manifested on the chart of a patient receiving 500 cc. of blood every 8 hours, it may be assumed that spontaneous cessation of the hemorrhage is unlikely and surgery should be considered.

3. **A progressive drop in the red cell count, hemoglobin and hematocrit determinations.** Hemodilution may continue for a day or longer after bleeding has ceased, if the hemorrhage has been severe, but a continued fall in serial determination over a period of days is evidence that conservative measures have not checked the hemorrhage.

4. **Recurrent hematemesis or melena.** Hematemesis in particular (or fresh blood recovered from gastric syphonage) gives first hand evidence of persistent hemorrhage. It is easy to overestimate the total blood lost in this manner, since it is invariably diluted with gastric juices and sometimes with ingested fluids. Repeated hematemeses in a period of a few hours, particularly when coupled with evidence of an unstable circulation, indicate that conservative treatment is not succeeding. Melena is a far less reliable sign, unless the patient is having stools every few hours; the latter is likely to be the case if a rapid hemorrhage is in progress.

Contraindications to Emergency Operation

1. **Unknown source of bleeding.** The principle objective of an operation is to eradicate a localized source of the hemorrhage; this will usually be a duodenal or gastric ulcer, and less frequently a gastric neoplasm. The suitable operation is almost always a gastric resection, with direct control of the bleed-

ing in a duodenal ulcer if it cannot be resected with the stomach. Emergency operation is of no value in bleeding from esophageal varices, and its usefulness in gastritis with severe hemorrhage is still debated. Since esophageal varices and gastritis together account for about 15 per cent of all massive upper gastrointestinal hemorrhage, it is generally unwise to operate unless the lesion has been previously localized and identified by x-ray. It is therefore sometimes advisable to precede an emergency operation by an emergency x-ray, to determine by barium study if esophageal varices are present; if present, they are the presumptive source of hemorrhage, and other measures such as esophageal tamponade are in order. Although some surgeons will operate with a clinical diagnosis of duodenal ulcer, even if x-ray evidence is lacking, this is a risky procedure; it is perhaps safer for the patient to be maintained on a conservative regimen with the rate of transfusion increased to keep pace with the bleeding.

2. **Advanced coexisting disease.** Not infrequently massive hemorrhage (even from a duodenal ulcer) is a more or less terminal event in patients suffering from such diseases as chronic nephritis, severe hypertension, or leukemia. Emergency operation in such patients is hopeless and meddlesome.

3. **Enormous obesity.** Every surgeon is familiar with the greatly increased technical difficulties encountered in the obese, and there is a widespread impression that operative risk is increased also. In rare instances one may be justified in refusing to operate for these reasons.

Case Reports

Case 1. Hemorrhage from duodenal ulcer; recovery without operation. A 53 year old Greek restaurant owner was admitted to the Clinic Hospital on February 6, 1950, for emergency treatment of severe bleeding from the upper gastrointestinal tract. Within a period of 12 hours preceding his admission he had vomited blood, passed a tarry stool and fainted twice. He had suffered from periodic epigastric distress for about 5 years, and for about 1 year he had been taking baking soda to relieve his discomfort. There had been no previous hemorrhages and there had been no gastrointestinal x-ray studies. At the time of admission the physical examination revealed a cheerful, moderately obese middle-aged white man whose general condition appeared to be good. The blood pressure was 110/70 and the pulse rate 100. The abdomen was soft and nontender, there were no masses, and the liver and spleen could not be palpated. Tarry feces were present in the rectum. The red cell count was 4,100,000, the white cell count was 10,550 and the hemoglobin was 10.5 Gm. per 100 cc.

The patient was given a single transfusion of 500 cc. whole blood shortly after his admission, largely on the basis of the history (fig. 1). He was started on an ulcer feeding regimen with gelusil. A few hours after his transfusion the patient had a copious hematemesis (measured at 1100 cc.), passed a small, dark stool, the pulse rate rose to 122 and the blood pressure dropped to 88/64. Within the next 6 hours he received an additional 1500 cc. of whole blood with a satisfactory clinical response. Recovery was steady without further evidence of bleeding. Barium x-ray studies showed a constant deformity of the duodenum. He was discharged 14 days after his admission on a strict ulcer regimen. The patient was doing well when last seen 6 weeks after operation.

Comment. The patient presented a typical problem. This was an initial hemorrhage in an obese patient past 50 years of age, severe enough to have

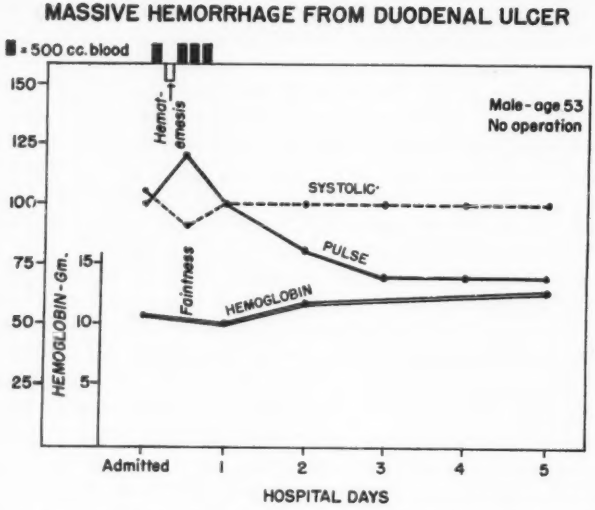

Fig. 1. Case 1. Schematic course of patient with sudden massive hemorrhage from duodenal ulcer. Conservative treatment.

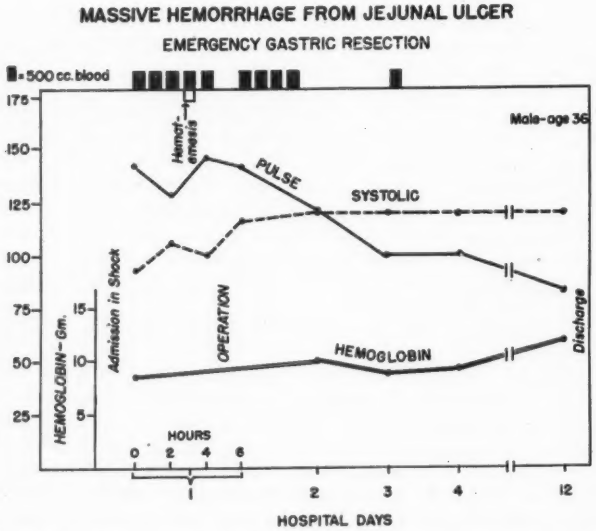

Fig. 2. Case 2. Schematic course of patient with sudden massive hemorrhage from jejunal ulcer. Emergency operation.

caused him to faint at home, and to reduce his blood pressure to shock levels shortly after he had been admitted. The source of the bleeding was not known, although the history suggested a duodenal ulcer. He needed 2 liters of blood to overcome the effects of the hemorrhage; this was given within the first 18 hours of his hospitalization. Had he required more blood that first day, or if he had bled again on ensuing days at a rate sufficiently rapid to compromise the stability of his circulation, an emergency operation would have been done, preceded by an emergency x-ray to rule out esophageal varicosities. As it was, the more desirable course could be followed—that of permitting the hemorrhage to cease spontaneously. Since this patient had never had systematic treatment for his duodenal ulcer, the gastroenterologist and surgeon agreed to follow his progress under ulcer management, and postpone surgical intervention indefinitely.

Case 2. Hemorrhage from jejunal ulcer; recovery after emergency gastric resection. A 36 year old single welder was admitted to the Clinic Hospital on January 3, 1950 for emergency treatment of a massive hemorrhage of 2 days' duration. He had had "stomach trouble" since the age of 18, and at the age of 30 a gastroenterostomy had been performed elsewhere for pyloric obstruction. For 2 weeks prior to admission he had been so weak that he had been unable to work. For 2 days he had been vomiting blood and the previous day had passed several tarry stools. He had been given a single blood transfusion at another hospital. Examination on admission revealed a pale, perspiring, apprehensive white man with a pulse rate of 144 and a blood pressure of 86/40. The abdomen had the scar of previous surgery, but was otherwise normal and showed no masses or tenderness when lightly palpated. The red cell count was 2,900,000, the white cell count was 16,800 and the hemoglobin 8 Gm. per 100 cc.

Whole blood transfusions were started promptly and the patient received 2000 cc. within the next 4 hours (fig. 2). The pulse rate dropped to 108 and the blood pressure rose to 118/68. Shortly after this, however, he vomited 400 cc. of bloody material, the pulse rate rose again to 144 and the blood pressure dropped to 100/70. An additional 500 cc. of whole blood was started and the patient was taken to the operating room. Under general anesthesia the abdomen was opened and a large, actively bleeding vessel in a jejunal ulcer promptly ligated. Immediately following the control of the bleeding he was given 2000 cc. of blood by arterial transfusion, and a subtotal gastric resection was carried out, with a jejunostomy for feeding purposes. His condition at the conclusion of the operation was better than it had been at the start. The patient received one more blood transfusion on his second postoperative day (making a total of 5000 cc.) and was discharged on the eleventh postoperative day with a red cell count of 4,200,000 and a hemoglobin of 12 Gm. per 100 cc.

When last seen 2 months after the operation his weight had increased 21 pounds and he was symptom-free.

Comment. This patient, in the opinion of all the physicians who examined him, would have died from exsanguination had there been no surgical intervention. It was a safe assumption, based upon the previous surgery, that the source of the bleeding was a jejunal ulcer, even though there was no direct x-ray evidence. Despite his comparative youth, there is little likelihood that the bleeding from a large branch of the middle colic artery (involved in the jejunal ulcer) would have stopped spontaneously. Although he was desperately ill at the time of operation, once the bleeding had been surgically arrested and his

blood volume restored by arterial transfusion, he easily withstood a complicated procedure rendered more difficult by the previous gastroenterostomy.

Case 3. Chronic and acute hemorrhage from duodenal ulcer; recovery after emergency gastric resection. A 59 year old Italian carpenter was admitted to the Clinic Hospital on January 20, 1950 for treatment of periarthritis of the left shoulder. He had had a known duodenal ulcer for at least 6 years, and passed occasional black stools. While undergoing hospital treatment for his shoulder he developed an exacerbation of his ulcer symptoms, and it was found that the red cell count was 2,200,000 and the hemoglobin 4 Gm. per 100 cc. A strict ulcer regimen was instituted and between January 26 and January 30 the patient received a total of 2750 cc. whole blood transfusions. This raised his hemoglobin level to 9.5 Gm. per 100 cc. On January 30, however, he passed a grossly bloody stool, the pulse rate rose to 120 and the blood pressure dropped temporarily to 80/50. He was taken to the operating room several hours later, and a subtotal gastric resection was carried out. A catheter duodenostomy was also

Fig. 3. Case 4. Leiomyoma of stomach which produced massive hemorrhage. Local resection spared the stomach.

performed (as advocated by Welch when the closure of the duodenal stump is difficult). Vessels in the ulcer bed were ligated, although there was no active bleeding at the time the ulcer was exposed. He received 1000 cc. of whole blood during the operation and a single transfusion of 500 cc. of blood on the third postoperative day. Recovery was entirely uneventful. It was possible to re-institute active treatment for the shoulder on the seventh postoperative day, and he was discharged asymptomatic on the thirteenth postoperative day with a hemoglobin of 10.8 Gm. per 100 cc. When last seen 2 months after the operation he had no gastrointestinal complaints.

Comment. This patient had a slow but persistent hemorrhage from a known duodenal ulcer which failed to respond to intensive treatment under hospital conditions. A single episode of weakness with a drop in blood pressure following the passage of a grossly bloody stool 4 days after treatment had been

instituted was sufficient indication for surgery. While the bleeding was not as dramatic as that in the 2 preceding cases, and while it is conceivable that it might have stopped after a few more days of treatment, it seemed wise to arrest the hemorrhage and perform a definitive operation for the ulcer rather than run the risk of further bleeding and possible death. This case further demonstrates the fact that under modern conditions one may operate safely long after 48 hours of bleeding (a procedure once frowned upon by surgeons generally) and that in some instances it may be advisable to do so.

Case 4. Hemorrhage from gastric leiomyoma; spontaneous arrest; elective resection. A 49 year old white machinist was admitted to the Clinic Hospital on January 21, 1950 for emergency treatment of a painless gastrointestinal hemorrhage. For 5 days he had been passing tarry stools and feeling progressively weaker. Although "indigestion" had been present for 20 years, he had never before experienced bleeding. On admission the patient was pale and apprehensive, the pulse rate was 100 and the blood pressure 110/64. General examination was otherwise normal. He received 1500 cc. of whole blood transfusions in the next 36 hours following which his hemoglobin was 8.2 Gm. per 100 cc. Bleeding appeared to have ceased. An additional 2500 cc. of blood in the next 8 days raised the hemoglobin to 14 Gm. per 100 cc. Gastroscopic study showed the source of the bleeding to be a large and presumably benign neoplasm in the proximal third of the stomach, and this was confirmed by the roentgenogram. The patient was discharged to attend to some personal business, and readmitted on February 6, 1950. A local resection of a benign gastric leiomyoma was performed on the following day (fig. 3). Recovery was uneventful, and he was discharged on the ninth postoperative day. When last seen, 2 months after operation, the patient was asymptomatic.

Comment. This patient had a slow but persistent hemorrhage from a lesion undiagnosed at the time of admission. The hemorrhage responded to blood transfusion and the usual conservative measures. Delay permitted an accurate localizing diagnosis, and a carefully planned interval operation which could be executed with a minimum of risk.

Summary and Conclusions

Although it is desirable to permit a massive hemorrhage from the upper gastrointestinal tract to subside spontaneously if possible, an occasional patient will require an emergency operation to arrest the bleeding, Satisfactory management of patients with massive hemorrhage requires the liberal use of blood transfusions. Close cooperation between internist and surgeon is needed to insure prompt recognition of the few requiring surgical intervention.

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HODGKIN'S DISEASE AND PREGNANCY

Report of 4 Cases

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DOES pregnancy cause exacerbations of Hodgkin's Disease? In 1888, when Wright[1] reported the first known instance of Hodgkin's disease complicating pregnancy, and until 1948 when Summers and Reid[2] gave their account, this question has been debated and several individual cases have appeared in the literature. Perrier[3] described 5 instances and Gilbert[4] 7 pregnancies in 5 patients. Our report concerns 4 proven cases of Hodgkin's disease observed at the Cleveland Clinic between 1930 and 1949, and associated with known pregnancy during the course of the disease.

Case Reports

Case 1. A woman, aged 21, was first seen at the Clinic on July 24, 1930. Her chief complaint was dyspnea. Six months previously she had had pleurisy with effusion following a cold. She had undergone numerous thoracenteses but the fluid had reformed so rapidly that her dyspnea was relieved only for a day or so after aspiration.

Our examination disclosed adenopathy in the left supraclavicular and axillary lesions. The entire chest on the left side was flat to percussion and the heart displaced to the right. A roentgenogram showed complete opacification of the left side of the chest with displacement of both heart and mediastinum into the right thoracic cavity. A diagnosis of Hodgkin's granuloma was made by biopsy of an axillary node.

Thoracentesis of about 2000 cc. daily was required (between July 24, 1930 and August 12, 1930) in order to relieve dyspnea. The fluid was a cloudy yellow and contained numerous lymphocytes. Roentgen therapy was given to the anterior and posterior mediastinum, and to the left supraclavicular and left axillary regions.

The patient was free of symptoms for 3 years until 1933 when she returned complaining of back pain. There was no dyspnea, although a partial hydrothorax was present in the left side of the chest. No enlarged nodes were demonstrable. Her chest on the left was again irradiated anteriorly and posteriorly.

The patient was not heard from until June, 1937, at which time she had been delivered of a full term baby at another hospital. This was 7 years after her first admission to the Clinic and 4 years after the last treatment. The pregnancy had been presumably uneventful; however, during her stay in the hospital a mass in the left axillary region was discovered. Roentgen therapy was given with apparently satisfactory results.

Six months later the patient entered the same hospital complaining of dyspnea, fatigue, reappearance of a mass in the left axilla, and severe pruritus of the legs. The symptoms were of 2 months' duration. She was described as obese and pale. A firm non-tender mass was attached to the left lower chest wall and a roentgenogram disclosed probable extension into the left lower lung. An electrocardiogram revealed

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inverted T waves in Leads 1, 2 and 3. This supposedly indicated infiltration of the pericardium and/or myocardium. Roentgen therapy was given over the tumor area and the patient was discharged.

Improvement was slow but the mass in the axilla gradually subsided; the patient improved and eventually became well enough to do housework. Roentgenogram in October 1938 showed considerable decrease in the size of the left thoracic mass.

She was again admitted to the hospital in April 1939 after a gradual relapse over a period of several months. She was semistuporous, orthopenic, and had generalized edema. The veins in her neck were engorged and no breath sounds were audible in the left side of the chest. A large firm mass in the left upper quadrant appeared to be attached to the skin and did not move on respiration. The electrocardiogram showed auricular fibrillation and low ARS waves. Supportive treatment, digitalis, and mercurial diuretics were administered without improvement and the patient died.

At autopsy a large grayish-white mass was found which exhibited irregular areas of necrosis, largely replacing and invading the left upper lung; the left hilar region was invaded and the pulmonary artery was surrounded by neoplastic tissue. There was encroachment on the wall of the left atrium with actual invasion of the muscle in several places; several nodules measuring 1.5 cm. were present on the endocardial surface. The coronary sinus in the left auriculoventricular groove was occluded by a tumor growing within the lumen. No pericardial effusion was present.

A second large hard mass, difficult to remove, was located in the left upper quadrant; it had invaded the lower ribs and dorsal vertebrae, the muscles in the back and subcutaneous tissue. The mass measured 28 by 15 cm. and weighed 2800 Gm. The splenic flexure of the colon was encased in neoplastic tissue and the left adrenal gland was largely replaced by tumor. The liver, spleen and kidneys were not involved. No tumor was found in the brain.

The histology of the tumor was similar in all affected areas, made up of fibrous tissue, fibroblasts, large and small areas of necrosis, giant cells, both polymorphonuclear and polynuclear, lymphocytes and eosinophils. The para-aortic lymph nodes showed complete destruction of structure crowded with the same type of cells already enumerated. Histologically this case must be accepted as one of Hodgkin's disease since the morphologic picture is fairly typical of the disease. Grossly large masses of tumors in the thorax and soft tissues of the abdominal wall are distinctly invasive in character. It might, therefore, be justifiable in this instance to refer to the disease as Hodgkin's sarcoma.

Comment

The patient had Hodgkin's disease for more than 9 years. A review of her original biopsy specimen shows it to be typical Hodgkin's granuloma. For several years the disease was not particularly malignant and apparently reasonably radiosensitive. It may be assumed that at some time, perhaps in the last year of her life, the Hodgkin's granuloma underwent transition to the sarcoma type. Such transition has been observed and reported by others.

Case 2. A married nurse was admitted to the Cleveland Clinic Hospital on April 30, 1943, complaining of fatigue, pronounced weakness, dyspnea and failure of vision. She believed herself to be about 5 months pregnant, the last menses having occurred on November 15, 1942.

One year previously she had become aware of fatigue and weakness and the presence of two enlarged glands in the neck. The adenopathy subsided without treatment after

an uncertain interval but weakness persisted. She was able to continue her profession until 2 months before admission when she became totally disabled with asthenia, dyspnea, and failure of vision; concomitantly cervical adenopathy reappeared.

The patient was obviously ill and the mucous membrane and skin were extremely pale, the latter having a faint icteric tint. Enlarged discrete nodes were present in anterior and posterior cervical regions, as well as in the axillary and inguinal regions. The spleen was large and firm with its inferior border at the level of the umbilicus. The pregnant uterus was thought to contain a 5-month fetus and fetal movements could be palpated. A roentgenogram of the chest showed no abnormality. The red blood count was 1,900,000; hemoglobin 4.7 Gm. or 30 per cent; color index 0.79; volume index 0.87; white blood count 7100; reticulocyte count 1 per cent; icteric index was 25 per cent. No abnormal white cells were present. Biopsy of a cervical gland showed Hodgkin's granuloma.

During her stay in the hospital she had a slight daily rise in temperature but never above 101 F. Eight transfusions of 500 cc. of whole blood were given. Extreme asthenia persisted. Irradiation was not attempted because of the continued poor condition of the patient and the generalized disease. At her request she was discharged. Death occurred on May 25, 1943, 1 month after hospital admission and before termination of pregnancy. No autopsy was performed.

Comment

A review of this patient's history indicates that from the onset of the disease to its termination there had been a continuous progression. Pregnancy may have hastened the outcome. It is unfortunate that a diagnosis was not made at an earlier date as the patient had not had the benefit of irradiation.

Case 3. A 24-year-old housewife was first seen at the Cleveland Clinic on May 25, 1943, complaining of swollen nodes in the neck associated with pain in the shoulders and neck. The discomfort had appeared about 4 months previously following delivery of her first baby, and adenopathy had been present for 1 month.

There was a single hard fixed mass in the left supraclavicular region but no definite adenopathy otherwise, and the spleen was not palpable. Red blood count was 3,980,000; hemoglobin 71 per cent; white blood count 9150; differential blood count normal. Roentgenogram of the chest disclosed large mediastinal nodes.

The patient had had a biopsy of a cervical node which disclosed Hodgkin's disease. She had been given roentgen therapy with satisfactory results.

The patient evidenced no further complaints until September 1946. At this time she was 5 months pregnant and a severe generalized pruritus had developed which continued unabated until the time of delivery December 22, 1946. Four roentgen ray treatments in the nature of a spray had been given without relief.

The patient was seen again in the Department of Dermatology at the Cleveland Clinic on February 11, 1947. Numerous excoriations and scars were present over the entire trunk and extremities as a result of almost continuous scratching. No palpable lymphadenopathy existed although a roentgenogram showed that the mediastinum was noticeably widened both to the right and left, presenting irregular nodular shadows consistent with Hodgkin's disease. She was given roentgen therapy to the anterior and posterior mediastinum and to an epigastric and midlumbar area field, after which the pruritus subsided promptly.

The patient manifested no further discomfort until August, 1947, when one large supraclavicular node was found. This swelling subsided after treatment. However,

pruritus reappeared in March, 1948, following which direct anterior and posterior mediastinal fields were irradiated. The pruritus subsided but a persistent cough remained. At this time no nodes were apparent in roentgenogram of the chest although infiltration was present, extending into left upper lobe.

The troublesome cough continued and in March 1948 infiltration of the left upper lung field had increased but no mediastinal adenopathy was apparent. A roentgenogram in May 1948 revealed a decrease in degree of infiltration in both lung fields, but also evidence of enlarged hilar nodes. As pruritus reappeared in October 1948, she was given roentgen therapy to the abdominal and lumbar areas.

Relief from pruritus was obtained, but when last seen on November 12, 1948, her general condition was obviously poor and the patient was considered in the terminal phase of the disease.

Comment

The patient survived for a 5 year period with Hodgkin's granuloma, the onset of which coincided with her initial pregnancy. A definite exacerbation of the disease occurred during her second pregnancy. Her children, however, are healthy.

Case 4. A woman, aged 23, was first seen at the Clinic on July 13, 1949. About 1 year previously, during her first pregnancy, she experienced difficulty in swallowing and occasional choking spells. Shortly thereafter she developed swelling of the lymph nodes of the neck followed by severe substernal pain. Fluoroscopic examination of the chest was made and a mediastinal mass was noted. The patient was given roentgen therapy to the chest and neck.

After delivery of a normal child, now 10 months old, a biopsy was made of a supraclavicular node which proved to be Hodgkin's disease of the granuloma type.

She returned to the Clinic because of progressive loss of strength and energy and return of respiratory distress. On examination moderately enlarged cervical lymph nodes were palpable. Roentgenograms of the chest showed some enlargement of the hilar nodes. Blood counts were normal as were other routine laboratory examinations.

The patient was advised to return for further roentgen therapy.

Comment

This patient developed the first manifestations of Hodgkin's disease when pregnant. Sufficient time has not elapsed for a prognosis.

Discussion

Inasmuch as Hodgkin's disease is unpredictable, one cannot assume that pregnancy will have either a deleterious effect on the course of the disease or a favorable influence on the outcome. Instances are reported wherein women undergo pregnancy without exacerbation of the disease.[5] Only 2 of Gilbert's 5 patients had any manifestations of the disease while pregnant.

From published reports one cannot conclude that pregnancy has any effects on the ultimate result. The general average survival of patients with Hodgkin's disease is about 2½ years; however, in our experience about 20 per cent live for 5 years. Epstein's[6] report of 500 collected cases in both sexes indicates that

the outlook for women is somewhat better than for men by about 1 year. Three of Perrier's group of 5 were living at least 4 years after their respective pregnancies.

The future condition of the offspring of the mother afflicted with Hodgkin's disease cannot be predicted. Adair[5] refers to the death of a 3½ month old infant born of a mother with Hodgkin's disease. The autopsy revealed a lymphoma of typical Hodgkin's type. There were 7 children in Gilbert's group without manifestations of the disease, the oldest 12 years of age, the youngest 3. One of our patients (Case 3) has 2 healthy children born during exacerbations of the mother's disease. The infant referred to in Case 1 cannot be traced while the 6 month fetus in Case 2 died with the mother.

Although marriage and pregnancy for women with Hodgkin's disease are inadvisable, as Gilbert says, "These events occur in spite of us." Inasmuch as a justifiable course is difficult to decide upon when pregnancy exists, individualization of cases is necessary. Abortion has been performed, followed by irradiation with favorable effect. Cesarean section followed by heavy irradiation failed to save another patient.

The patient, case 1, although having had Hodgkin's disease for 7 years prior to pregnancy, had no exacerbations during that time. However, soon afterwards her condition became progressively worse until death resulted. The original diagnosis was Hodgkin's granuloma and, at autopsy, Hodgkin's sarcoma.

The patient, case 2, was reasonably well for the first 5 months of pregnancy then became rapidly and progressively worse until death. The duration of disease apparently was less than 2 years.

The patient, case 3, first observed manifestations of Hodgkin's disease soon after delivery of her first child and there was probable exacerbation during her second pregnancy. She has survived 5 years and is still under treatment.

The patient, case 4, developed Hodgkin's disease early in pregnancy. It is questionable whether pregnancy influenced the disease.

Conclusions

Although a limited number of cases are presented they nevertheless call attention to the fact that pregnancy may result in exacerbations of Hodgkin's disease.

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CARCINOMA OF THE CARDIAC PORTION OF STOMACH

Treatment by Use of the Thoraco-Abdominal Approach

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SUCCESSFUL treatment of cancer arising in the cardiac portion of the stomach demands total extirpation of the cancer-bearing tissue within and adjacent to the stomach including the spleen, the tail of the pancreas, the lesser peritoneal sac, the great omentum, and the lymph nodes in the gastrohepatic ligament and in the infraduodenal area. Incomplete removal of these structures diminishes the chance of cure.

The need for more adequate exposure of the cardiac portion of the stomach prompted Von Mikuʹicz[1] to attempt transthoracic resection in 1896. The patient died. In 1916 Brunn[2] performed the first successful cardiectomy and esophagogastrostomy. The combined thoraco-abdominal approach was suggested by Janeway and Green[3] in 1910 but it was not until after 1933 that the feasibility of the combined thoraco-abdominal approach to the upper stomach and its adjacent structures was demonstrated by Oshawa.[4]

The development of the thoraco-abdominal incision has depended less upon the boldness of the surgeon than it has upon evolution of safe anesthesia. Management of the open thorax has become a commonplace procedure and in qualified hands does not increase the risk of operation.

Technic

The series of cases to be presented represents the combined experience of the authors in 22 operable cases of gastric carcinoma involving the cardiac end of the stomach. In each case the thoraco-abdominal approach was employed and some form of gastric resection was performed. As might be expected there was considerable variation in the operative procedures, some of which were essentially palliative. Increased familiarity with this approach has led to the simplification of what appeared to be a formidable procedure.

The patient's left side is tilted upward at an angle of about 45 degrees. The table may be tilted in the reverse direction during the exploration of the abdomen. The abdominal component of the incision should be made first and

the abdominal cavity explored to determine operability.[5,6] The laparotomy may be performed by various technics, using midline, left rectus, transverse, or oblique incisions. The simplest incision is the oblique type that begins near the midline and traverses the left rectus muscle to the costal margin in the same direction as the ribs (fig. 1). This small incision allows adequate exploration of the upper abdomen and may be extended in either direction without altering the position or the draping of the patient. If the thoraco-abdominal approach is indicated, the lateral aspect of the abdominal incision is continued through the costal arch and along the seventh or eighth interspace. Should the thoracic component of the incision prove unnecessary, the

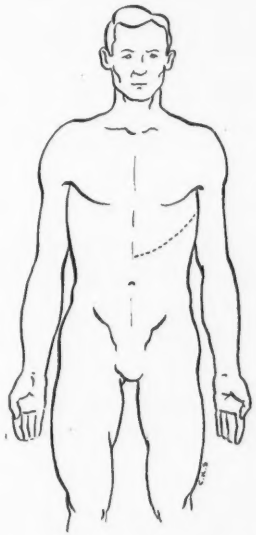

FIG. 1. Thoraco-abdominal incision.

medial limb may be continued across the midline to transect the right rectus muscle.

The determination of operability is based on inspection and palpation through the initial laparotomy incision. Particular attention is paid to the mobility of the tumor, and to the presence of metastases in the liver or on the peritoneum including that of the pelvis. Those patients who have numerous hepatic metastases, and those who have intra-abdominal fluid with peritoneal seeding, are considered to be beyond hope of cure or palliation. In these hopeless cases the exploratory procedure has been minimal and is associated with little morbidity.

After operability has been determined, the surgeon may elect to convert the incision into a combined thoraco-abdominal approach. The skin incision

is continued over the costal margin and through the appropriate interspace. There is wide variation in the configuration of thoracic cages and for this reason the selection of interspace must be individualized. We have usually employed the sixth, seventh, or eighth interspaces and resection of a rib has not been necessary. Following the skin incision the cartilaginous costal arch is incised; at least one pair of vessels parallels the arch and will require ligation. The intercostal muscles are divided and the pleural space entered. The wound edges are protected with drapes and the ribs are spread to aid exposure of the left upper quadrant and subdiaphragmatic area. If the terminal esophagus is to be resected the diaphragm is cut directly to the esophageal hiatus; if the esophagus is not involved, the diaphragm may be left intact or transected in part. The incision and subsequent repair of the diaphragm may be unnecessary in certain cases; if it can be avoided there is appreciable reduction in the operating time.

The excellent exposure afforded by the thoraco-abdominal approach allows the surgeon to evaluate the problem fully and to deal with it accurately. In the 22 cases presented several types of resection and anastomosis were employed.

Table 1

Surgical Procedures in 22 Cases Where the Thoraco-Abdominal Approach Was Employed

Number of Cases	Subtotal Resections	Total Resections	Excision of Polypoid Tumor
22	15	6	1

When the operation for a high gastric carcinoma is done not merely for the palliation, but with the hope of effecting a cure, it should include splen-

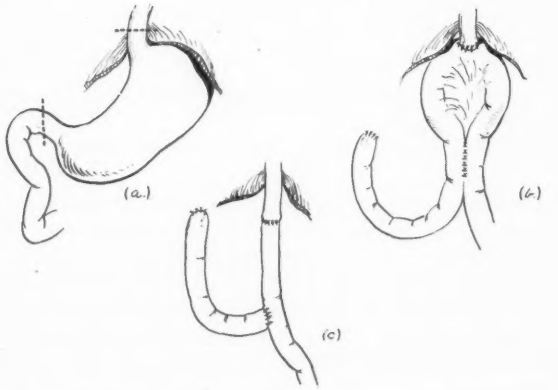

FIG. 2. (a) Total gastrectomy, indicating sites of transection. (b) Esophagojejunostomy, entero-enterostomy below. (c) Roux en Y type esophagojejunostomy.

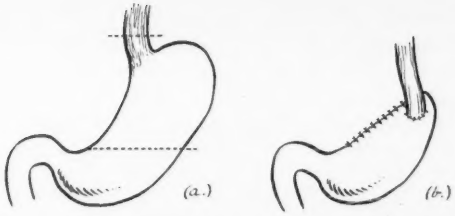

FIG. 3. Partial gastrectomy, indicating sites of transection. (b) Esophagogastrostomy, completed.

ectomy, resection of the tail of the pancreas, removal of a generous segment of the gastrocolic and gastrohepatic ligaments, removal of the great omentum, and resection of a portion of the terminal esophagus, in addition to extirpation of the cancer-bearing stomach. With proper exposure the dangers of blind dissection and uncontrollable hemorrhage are removed and the morbidity and mortality rates are lowered.

It is usually easiest to begin the resection by delivering the spleen and incising the peritoneum at its lateral border. The spleen, the splenic vessels, the stomach, the tail and body of the pancreas, are then mobilized from left to right in block, along with the great omentum and the peritoneum of the lesser sac. The operation is essentially a retroperitoneal one, the peritoneum being removed with the viscera of the upper abdomen. The pancreas is transected at the desired level and its stump closed with mattress sutures. The splenic vessels and the left gastric artery are ligated retroperitoneally when they appear in the field. The stomach is either removed completely or transected well below the lesion, taking care to remove as much as possible of the node-bearing tissue along its curvatures, in the gastroheptic omentum and below the duodenum.

Re-establishment of continuity following gastric and esophageal resection has been performed in two ways. If total gastrectomy is indicated, a loop of jejunum is brought through the left transverse mesocolon and esophago-jejunostomy performed with complimentary entero-enterostomy below the mesocolon. In one case, an end-to-end esophagojejunostomy was made with a Roux type jejunojejunostomy (fig. 2). When a partial resection has been performed the greater curvature of the pyloric antrum has been preserved and the lesser curvature resected; this creates a tube-like remnant of stomach. The esophagus is then anastomosed to a slit wound on the anterior wall of the greater curvature (fig. 3). In all cases an intestinal suction tube is left in place beyond the anastomosis.

Closure of the thoraco-abdominal wound is accomplished easily. The costal arch is re-established by two chromic catgut sutures through the severed cartilage and one or two catgut pericostal sutures. The chest incision may be closed with catgut, silk, wire, or cotton; the abdominal wound is closed with interrupted wire figure-of-eight sutures. It is not always necessary to employ water-seal suction drainage in the chest; thoracentesis during the early post-

operative period usually will suffice. A sump drain may be used in the upper abdomen, particularly when there has been a partial resection of the pancreas. Early ambulation is advised in all cases.

Discussion

Much has been written about the necessity for total gastrectomy as against subtotal resection in cancer of the stomach. It is not our purpose to discuss this controversial subject. Six of the 22 cases were treated by total gastrectomy because of the location and nature of the lesion. Perhaps more important than total resection is the removal of the areas of lymphatic extention with excision of potentially involved extragastric tissue in addition to a wide margin of clearance within the stomach itself.

Of the 2 deaths in the group of 22 patients, 1 was due to cerebral thrombosis on the seventh postoperative day, the other was attributed to leakage through a tiny hole in the esophagus nearly 2 cm. above the line of anastomosis. The cause of this hole could not be determined. Other complications are listed in Table 2. All were of comparatively minor importance and exerted little influence on the ultimate course.

Table 2

Complications

Type	Number	Result
Cerebral vascular accident	1	Fatal
Leakage through perforation above anastomosis	1	Fatal
Empyema	2	Healed
Stricture of anastomosis	1	Healed*

Sufficient time has not elapsed to evaluate the end results of treatment. We believe, however, that the thoraco-abdominal approach has increased the resectability of high gastric cancer and has enabled us to afford palliation, at least, to a group of patients we would have considered inoperable heretofore. Time alone will tell whether more patients with cancer of the stomach will be cured by these radical gastric resections. In any event the increased exposure afforded by the thoraco-abdominal approach may be an important factor in reaching this goal.

Summary

1. Twenty-two patients with carcinoma of the cardiac end of the stomach treated by thoraco-abdominal resection of the stomach are reported.

2. There have been 2 hospital deaths in this series.

3. The immediate results have been good and the morbidity of operation is low.

4. Sufficient time has not elapsed to evaluate the end results.

**Required secondary surgical procedure; patient recovered.*

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CLINICAL SIGNIFICANCE OF HEMATURIA WITH ILLUSTRATIVE CASE REPORTS

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HEMATURIA, or the presence of blood in the urine, is one of the more frequent symptoms of disease of the urinary tract.

It would seem obvious that this phenomenon would impress the physician and the patient with the necessity for an immediate, complete examination to ascertain the cause of the bleeding.

However, in most instances unfortunately the hematuria is intermittent in character, and when the bleeding subsides a false sense of security is established. The patient assumes he is well, that the bleeding was not of serious importance because of its spontaneous disappearance, and as his general health does not seem impaired, he appears justified in such presumptions. However, to the physician, the cessation of bleeding is not an indication that its significance can be disregarded or minimized or its importance lessened, and a delay in complete urologic investigation should not be permitted. Unfortunately in many instances the physician and the patient minimize the gravity of this symptom, and a surgical cure is no longer possible when the diagnosis is finally established.

The presence of blood in the urine, if only on one occasion, means the presence of organic disease in the genito-urinary tract. If this conviction is sustained by the physician, it will permit the establishment of an early diagnosis while the lesion is amenable to surgical treatment; to procrastinate, thereby deferring urologic survey, may result in the development of far advanced lesions beyond the hope of medical or surgical cure.

How frequently is this viewpoint disregarded? Kretschmer[1] in a review of 933 cases of hematuria stated that the average duration of hematuria, or the average time which elapsed between the initial attack and the time of examination was 2.39 years.

In 694 cases of cancer of the bladder I reviewed a few years ago,[2] hematuria was the initial symptom in 73.5 per cent. A diagnosis was established by cystoscopic examination in 10.8 per cent within 1 month after the attack of hematuria; 32.1 per cent within 5½ months; 51.7 per cent within 1 year. Thus the estimation revealed that, in 48.3 per cent, a cystoscopic study was not performed until more than 1 year had elapsed from the onset of hematuria.

Debenham[3] in a review of 742 cases concluded that papilloma and carcinoma of the bladder are the commonest causes of hematuria in men. Inflammatory conditions of the urinary tract contribute most frequently to hematuria in women.

Hematuria as a presenting symptom: In men there is a 50 per cent chance that hematuria is due to a papilloma or carcinoma of the bladder, in women the

cause is as likely to be inflammatory as neoplastic. When hematuria is the only symptom in a male patient there is a 2 to 1 chance that it is due to papilloma or carcinoma of the bladder. In women, the most common cause is renal calculi.

MacKenzie[4] presented a review of patients with the complaint of hematuria who entered the Royal Victoria Hospital in 1932. He stated that 20.24 per cent of the patients admitted to the Department of Urology passed urine containing blood. In 75 per cent of the cases the blood was caused by either tumor, infection, calculus or nephritis. In 96 per cent of the cases with hematuria, a causative lesion was found within the urinary tract and more than 40 per cent of these lesions were neoplastic.

Cahill,[5] in 1942 in a review of cases from the J. Bentley Squier Urological Clinic, stated that close to 40 per cent of the patients with hematuria had neoplasms involving some part of the urinary tract. Only about 13 per cent of the patients with upper urinary calculi complained of blood in the urine at some time or other. Bleeding in some form occurred in bladder tumor in 85.7 per cent. He concluded that hematuria is a grave symptom, and in the majority of cases is associated with tumor, infection or calculus.

Van Duzen,[6] in a review of 500 cases of hematuria, estimated the source of bleeding as follows: urethra 38 cases; prostate 59 cases; bladder 82 cases; ureter 75 cases, and kidney 172 cases.

Classification:

1. Hematuria in general disease.
   - A. Acute fevers: Tonsillitis, scarlet fever, rheumatic fever, etc.
   - B. Chronic infections: Endocarditis, malaria.
   - C. Blood dyscrasias: Purpura, leukemia, hemophilia, polycythemia vera.
   - D. Deficiency and dietary disease: Scurvy, liver deficiency.
   - E. Diseases of unknown etiology: Hodgkin's disease, hypertension or arteriosclerosis with renal involvement, periarteritis nodosa.

II. Hematuria due to intrinsic disease of the urinary tract.

- A. Renal.
  1. Calculi or crystals.
  2. Nephritis.
  3. Tumor: Capsular, parenchymal, pelvic.
  4. Infection: Acute or chronic including tuberculosis.
  5. Anomalies: Polycystic disease, horseshoe kidney, nephroptosis, etc.
  6. Trauma.
- B. Ureteral.
  1. Calculi.
  2. Infection.
  3. Stricture.
  4. Tumor.
- C. Vesical.
  1. Tumor.
  2. Infection.
  3. Calculi or foreign bodies.
  4. Ulcer.
  5. Trauma.

D. Bladder neck.
   1. Tumor.
   2. Prostate including seminal vesicles.

E. Urethral.
   1. Infection.
   2. Stricture.
   3. Tumor.
   4. Consequence of instrumentation.

III. Hematuria associated with extra urinary pathology.
   A. Acute appendicitis.
   B. Diverticulitis of the colon.
   C. Neoplasm of the colon, rectum or pelvic structures.
   D. Acute or chronic salpingitis.

This classification is by no means exhaustive. Practically every disease of the urinary tract at some time or other may be accompanied by hematuria. The tabulation, however, illustrates the extensive investigation frequently essential to determining the etiologic factor producing blood in the urine.

A carefully elicited history is of utmost importance. Is the hematuria initial in type? If so it probably originates in the anterior urethra. Terminal hematuria arises from the posterior urethra or bladder. When the blood and urine are well mixed, the hematuria is usually of bladder, renal, or ureteral origin.

When associated with interruption of the urinary stream, hematuria suggests a tumor of the bladder neck. A history of recent laryngitis or tonsillitis implies an infection may be the source of bleeding. Pleurisy or a chronic cough and night sweats provoke a suspicion of tuberculosis.

Many other diseases such as purpura, hemophilia, and polycystic renal disease may be suspected from information volunteered by the patient.

The physical examination may reveal the presence of an enlarged spleen or indicate that one or both kidneys are palpable.

The vaginal and rectal examination may disclose the presence of a malignant lesion which explains the source of the blood.

Complete laboratory study, cystoscopy and pyelography usually suffice to establish an accurate diagnosis.

The diagnosis of essential hematuria should be made only rarely. Close cooperation between the internist and urologist is frequently essential to determine the cause.

The following case histories are presented to illustrate the similarity of symptoms and to re-emphasize the gravity of blood in the urine.

Case Reports

Case 1. A farmer, 31 years of age, entered the Cleveland Clinic complaining of blood in the urine which he had observed on two occasions in the preceding 3 months. The bleeding was not profuse, and the blood was completely mixed with the urine. The condition persisted for 2 days on each occasion and subsided spontaneously. There were no other symptoms and physical examination was normal. Retrograde

pyelography revealed a tumor at the upper pole of the left kidney. A nephrectomy was performed, and the final diagnosis was hypernephroma of the kidney.

This patient evidenced no symptoms aside from the two manifestations of mild hematuria. The diagnosis was established early in the course of the disease. Pain and tumor, indicative of a renal neoplasm, were absent. The gross specimen revealed no evidence of involvement of the veins and the patient has a reasonable chance for a cure.

Case 2. A 52-year-old accountant entered the Clinic complaining of pain in the right side and a persistent cough. The pain was constant, dull, aching, and boring-like in character with an occasional acute exacerbation. He stated that 6 months previously he had observed blood in the urine for 1 day. He consulted a physician a week later at which time the urine was clear. A specimen was secured, and he was told he had ruptured a vessel in his bladder. Medication was prescribed and since that time blood has appeared in the urine on only one occasion.

A mass was palpable in the region of the right kidney. The retrograde pyelogram diagnosis was hypernephroma of the right kidney and the roentgenogram of lungs revealed extensive metastasis. The lesion was obviously inoperable. The presence of a urinary tract disease was indicated by the detection of blood in the urine 6 months previously. The clinical significance of hematuria was disregarded and the patient was not given the benefit of a cystoscopic survey. When this was eventually secured the tumor of the kidney was inoperable. This case forcefully illustrates the necessity of cystoscopic study in a patient who has passed or is passing blood in the urine.

Case 3. A 57-year-old man entered the Clinic complaining of blood in the urine. The first attack of hematuria occurred 7 years previously and lasted 3 to 4 months. Two years ago blood was again observed in the urine and this time it persisted for 3 months when it again subsided spontaneously. At the time of our examination, hematuria had been present for 6 months, but was not associated with other urinary symptoms. The patient's diet had always been deficient in fruit and vegetables. Complete examination, including pyelography, failed to disclose an organic lesion. A diagnosis of scurvy was made. In addition to increasing the fruit and fruit juices in the diet, 2 tablets of cevitamic acid, 100 mg. were prescribed after meals. Satisfactory results were obtained from this treatment.

In this case, aside from red cells in the specimens of urine from the kidneys, the urologic examination revealed nothing abnormal; complete studies of the blood failed to show any blood dyscrasia. The final diagnosis was scurvy, and the symptoms disappeared following dietary adjustment.

Case 4. A man, 51 years of age, entered the Clinic complaining of hematuria and an aching pain in the right renal area. Two years previously he had passed a small calculus; hematuria had been present at the time. Two weeks before admittance he had observed blood intermittently in the urine, and a few days later developed an aching pain in his back.

A roentgenogram of the renal areas failed to disclose a calculus. The retrograde pyelogram revealed a round filling defect in the pelvis of the right kidney. The diagnosis of a nonopaque stone in the pelvis of the right kidney was confirmed at the time of operation.

Case 5. A woman, 31 years of age, entered the Clinic with the complaint of blood in the urine which was first noted 2 months previously and had been present intermittently since. There were no other urinary symptoms. The retrograde pyelogram revealed the presence of tuberculosis of the right kidney and acid fast organisms were isolated from the urine collected from this kidney.

The diagnosis was confirmed by operation.

Case 6. A man, 66 years of age, entered the hospital complaining of difficulty in voiding and the presence of blood in the urine. The patient had been aware of nocturia and frequency and decrease in the force of the urinary stream for 2 years. For a period of 3 weeks blood had accompanied urination, often profuse, and clots were passed. He experienced no pain or other urinary symptoms.

Cystoscopic examination revealed the presence of prostatic varices. Fulguration of the varices was accompanied by complete relief from symptoms.

Case 7. A 33-year-old woman entered the Clinic complaining of blood in the urine and swelling of the feet. These symptoms followed an episode of sore throat which had been treated by sulfadiazine and injections of penicillin. A diagnosis of hemorrhagic Bright's disease had been made elsewhere and a dietary regime was instituted and medication prescribed. The edema subsequently subsided but intermittent hematuria persisted for more than a year.

At the time of examination at the Clinic the blood urea was 39 mg. per cent. Addis counts, urine studies and the urea clearance test confirmed the diagnosis. In view of the hematuria a cystoscopic examination was performed which revealed a grade 1 papillary carcinoma of the bladder, later removed by transurethral resection.

In this instance there were co-existing pathologic lesions and the carcinoma of the bladder had been overlooked for a period of a year.

Case 8. A woman patient was registered at the Clinic in 1933 at which time a diagnosis of rheumatoid arthritis was made. She returned in 1942, at the age of 33, with the chief complaint of severe weakness. General physical examination was essentially negative except for pronounced pallor. The spleen was not palpable, nor was there lymphadenopathy.

Blood studies showed a hemoglobin of 35 per cent; the red blood count was 1,780,000. Urinalysis showed many red blood corpuscles.

On undertaking further blood studies, fragility tests showed increased hemolysis; the smear revealed spherocytosis, and auto-agglutination of the red cells; the white blood count and differential study were normal; red cell volume was 40 per cent of normal; reticulocytes were 25.8 per cent; icterus index was 38; sternal puncture showed a hyperplastic marrow. The final diagnosis was acquired hemolytic anemia. A splenectomy was performed.

This patient presented a pronounced microscopic hematuria. Urologic investigation failed to reveal a lesion in the urinary tract. Laboratory tests disclosed the cause of bleeding from the urinary tract, and the hematuria subsided following splenectomy.

Case 9. A 56-year-old farmer entered the Clinic complaining of blood in the urine. Six months previously, following an afternoon of pitching hay, he first observed hematuria. Blood was present in the urine on 2 occasions and then subsided spontaneously. A few days later he consulted a physician and medication was prescribed. He remained free of symptoms until 1 week before admittance when blood again appeared in the urine. There were no other symptoms.

Cystoscopic examination revealed an extensive malignant growth in the bladder. This was treated by transurethral resection and implantation of radon seeds.

If a cystoscopic examination had been made at the time of the first attack of hematuria *the patient could have had* the benefit of early treatment.

These case reports are included to illustrate the futility of attempting to diagnose the cause of hematuria without cystoscopic examination and complete laboratory study. Delay in performing such studies endangers the outcome of the disease, inasmuch as serious lesions may be overlooked.

Conclusions

Hematuria is neither a disease nor a clinical entity; it is a serious symptom that requires complete urologic investigation.

The physician assumes the responsibility and obligation of proving beyond a doubt that a serious lesion is not present in the genito-urinary tract.

In a series of 798 consecutive cases of hematuria in the records of the Department of Urology at the Cleveland Clinic, 59 per cent of the patients were suffering from tumors in the urinary tract, renal tuberculosis or calculus disease.

The presence of minimal or profuse bleeding, which may be persistent or intermittent in character and with or without accompanying pain, is usually of grave significance. An early determination of the causative factor is necessary in rendering a favorable prognosis.

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MASSIVE VITAMIN B_{12} THERAPY IN PERNICIOUS ANEMIA

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RICKES[1] and his co-workers and Smith[2] in 1948 simultaneously reported the development of a new material which they had isolated and found to be of value in the treatment of pernicious anemia. Numerous reports have appeared in the literature since this initial introduction of vitamin B_{12} to the medical profession. It is now generally recognized that the parenteral administration of this crystalline material commercially obtained from Streptomycin griseus is equally effective as liver extract in controlling the hematologic and neurologic manifestations of pernicious anemia.

A patient with neurologic manifestations of pernicious anemia was given massive parenteral injections of vitamin B_{12}* to determine whether a more rapid response could be obtained than with conventional methods of therapy.

Case Report

A white housewife, 65 years of age, was first seen at the Clinic on October 10, 1949, with the chief complaint of difficulty in walking since a stroke 3 years before. In 1947 there had been an abrupt onset of inability to use the right arm and leg satisfactorily following a fall. Since that time she complained of difficulty in maintaining her balance and of numbness of both legs and the right arm. One week prior to admission she dislocated her right shoulder. The dislocation was reduced without difficulty. The patient's past history and that of her family were noncontributory; she denied any history of anemia.

Physical examination revealed an elderly, obese patient not appearing acutely ill. Her blood pressure was 190/110, pulse 100 and regular, temperature normal. The skin and mucous membranes disclosed no significant pallor, icterus or cyanosis. The tongue showed slight atrophy about the edges. The examination of the heart, chest, lungs, and abdomen was normal. The cranial nerves were normal. There was a peculiar limping gait favoring the right leg. The Romberg sign was equivocal. The deep tendon reflexes were normal, with the exception of the achilles tendon reflexes which were absent. Moderate hypesthesia was noted below the knees and vibratory sensation was absent. The clinical impression was arteriosclerosis with hypertension and residual changes of cerebrovascular accident.

The red blood cell count was 3,560,000 per cu. mm., the hemoglobin was 9.8 Gm. per 100 cc. or 64 per cent of normal, the volume index was 1.03, color index 0.90, the white blood cell count was 3850 with a normal differential. The reticulocytes were 1 per cent. The icteric index was 4. The stained film revealed moderate anisocytosis and poikilocytosis. A routine urinalysis was normal. The blood sugar was 95 mg. per cent 5 hours after eating. The blood Wassermann and Kahn reactions were negative.

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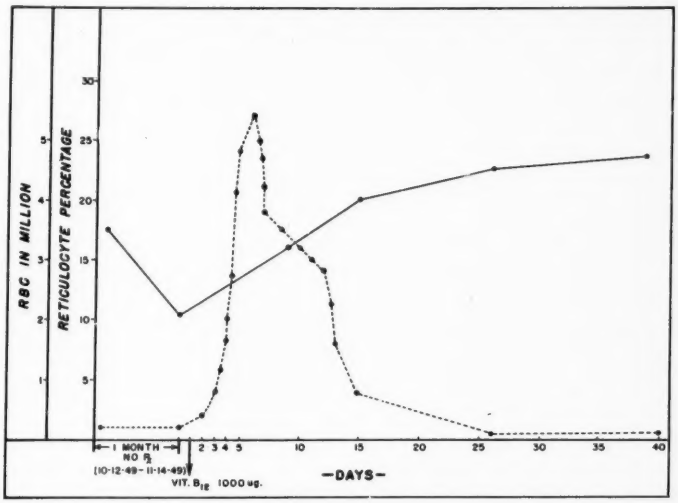
The x-ray examination of the chest was normal, with the exception of moderate left ventricular enlargement and calcification of the arch of the aorta. The electrocardiogram revealed a left bundle branch block.

The patient was unable to remain for further studies or treatment so she was urged to return at her earliest convenience. She returned exactly 1 month later at which time she was unable to walk without assistance. Pallor of the skin and mucous membranes was clinically evident. The Romberg sign was positive and the vibratory sensation was absent below the waist. The biothesiometer test (quantitative vibratory determination) revealed a complete loss of vibratory perception below the iliac crest. There was no urinary bladder disturbance. The patient was admitted to the hospital and the diagnostic procedures were completed. The red blood cell count was 2,180,000, hemoglobin 6.5. Gm. (42 per cent of normal), volume index 1.07, color index 0.95. The white blood cell count was 2800. The reticulocytes were 1 per cent. The icteric index was 5. The stained blood film revealed severe anisocytosis with macrocytosis. Many of the granulocytes were hyperlobulated. The platelets were diminished. The bone marrow obtained by sternal aspiration was megaloblastic. The gastric analysis revealed an absence of free hydrochloric acid. The remainder of the laboratory studies were normal.

On November 14, 1949, the patient was given 1000 micrograms of vitamin B_{12} intramuscularly and maintained on the regular hospital diet. An entirely satisfactory hematologic response was obtained (Table). Within a few days subjective improvement was noted in her appetite and sense of well being. In 1 week's time she was able to remain out of bed for several hours and to walk with minimal assistance. Two weeks following the administration of vitamin B_{12}, there was distinct improvement in her walking ability although a re-check of the quantitative vibratory determination showed no change. Progress visits and examinations were made in the fifth, seventh, eighth, and thirteenth weeks following the initial injection of vitamin B_{12}. By the thirteenth week she was remarkably improved in her walking ability and was able to walk without the assistance of crutches or a cane. At this time the position sense and epicritic sen-



sation of the feet and toes were normal. The vibratory sensation showed no appreciable improvement. She continued to complain of numbness, tingling and burning of her feet and, to a lesser extent, of her hands.

On February 6, 1950, approximately 13 weeks following the first injection of vitamin B_{12}, she was given a similar dose of 1000 micrograms of vitamin B_{12} intramuscularly. Progress examinations at monthly intervals showed slow though continued improvement in her walking ability, but no appreciable change in vibratory perception. Progress blood counts have been entirely normal.

Discussion

A patient with severe and progressive posterolateral sclerosis was selected for the administration of huge clinical doses of parenteral vitamin B_{12} to determine if these changes could be more rapidly and completely relieved than by the conventional method of daily injections of small doses. The hematologic response was entirely satisfactory with the single injection of 1000 micrograms of vitamin B_{12}. The neurologic manifestations showed a gratifying response and the subjective and objective degree of improvement appeared to be greater and more rapid than one would expect with the daily injections of vitamin B_{12} over the same period.

There is no way of determining the actual deficiency in liver units or micrograms of vitamin B_{12} which exists in patients with pernicious anemia. The clinician is forced to give treatment in excess of the actual deficiency.

The fate of parenterally administered vitamin B_{12} is not clear. There is evidence that part of it is excreted unchanged in the stool and urine. An undetermined percentage of the unaltered vitamin B_{12} is stored in the liver. The metabolic or enzymatic changes of vitamin B_{12} are unknown. There is no satisfactory method to determine how long the vitamin B_{12} remains in the liver or other tissues. It is possible that preparation of a satisfactory radioactive vitamin B_{12} will aid in clarifying the metabolism of this compound.

To date the parenteral injections of large doses (1000 micrograms) of vitamin B_{12} have not produced any local or systemic toxic effects in this patient or in several others under observation. No evidence of allergy or skin sensitivity has been noted.

We believe that the further clinical trial of large doses of vitamin B_{12} in patients with neurologic manifestations associated with pernicious anemia is warranted.

Summary

A patient with pernicious anemia having severe posterolateral sclerosis was treated with large parenteral doses of vitamin B_{12}. Improvement of the neurologic manifestations appeared to be more rapid than is usually observed in patients treated by conventional methods.

References

1. Rickes, E. L. et al. Crystalline vitamin B_{12}. Science **107**:396 (April 16) 1948.
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URINARY TRACT DISORDERS

The following abstracts conclude the proceedings of the course on Medical and Surgical Disorders of the Urinary Tract presented by the Frank E. Bunts Educational Institute on November 17, 1949. The first portion of these proceedings appeared in the April issue of the Cleveland Clinic Quarterly.

DIETARY MANAGEMENT OF UREMIA

G. M. C. Masson, Ph.D.

A study was conducted to test experimentally the effects of high iso-caloric carbohydrate, fat, and protein diets and the effect of hormones (desoxycorticosterone acetate and free testosterone) on survival times and azotemia (blood urea N) in bilaterally nephrectomized rats. All treatment was begun at the time of nephrectomy. Survival was definitely improved and azotemia greatly diminished by administration of fat or carbohydrate rather than protein.

Treatment with hormones had no significant effect on survival time regardless of diet, and little effect on azotemia. Neither did diets nor hormones effect the evolution of uremia in nephrectomized rats subjected to simulated infection (turpentine abscess).

These experiments substantiate the beneficial effects claimed by Borst for the treatment of uremia by administration of a high caloric diet, composed largely of carbohydrate. They do not confirm the suggestions of others that hormonal treatment is of value after nephrectomy.

CYSTITIS AND INTERSTITIAL CYSTITIS

J. G. Warden, M.D.

The etiologic agents of cystitis may be grouped into 4 main classes: (1) The nonbacterial agents including both chemical and mechanical; (2) Bacterial including chronic, tuberculous, and the rarely luetic lesions; (3) Yeast fungi; (4) Animal parasites.

The symptoms are:

1. As a general rule the patient's attention is directed to the inflamed bladder by varying degrees of urinary frequency and the severity is usually indicative of the severity of the disease. Frequency experienced during the day but not at night generally indicates a physiologic rather than a pathologic process.

2. Pain occurs in varying degrees depending upon the acuteness of the cystitis. Usually pain is more severe during the act of urination or it may be terminal in type.

3. In the early stages of bacterial cystitis the urine is only slightly turbid. Later on there is pronounced turbidity with clumps of pus cells on microscopic examination. However, it cannot be overemphasized that absence of pyuria does not eliminate the presence of organic bladder disease.

4. The pain of complete urinary retention is usually referred to the suprapubic region. In acute cystitis in the male, the pain is referred to the tip of the penis, to the perineum, and along the inguinal ligaments to the rectum and low back region.

5. In the presence of acute cystitis the urine may be tinged with blood and occasionally the bleeding may be diffuse.

A clinical diagnosis is established by a history of frequency, pain, and pus in the urine. Because cystitis often represents a secondary rather than a primary vesical lesion, conservative treatment frequently fails to alleviate the patient's symptoms. Therefore, in cases which do not subside within a period of 10 days to 2 weeks following adequate conservative treatment, complete urologic investigation is indicated.

The treatment of cystitis with the various chemotherapeutic agents is dependent

upon the type of invading organisms. However, without specific diagnosis, the treatment of any extended or recurrent bout of cystitis with an antibiotic chosen at random is to be condemned.

The etiology of interstitial cystitis is not known but foci of infection, circulatory impairment, and lymphatic obstruction have been suggested. Hunner ulcer is predominantly a disease of women, with an occurrence of approximately 94 per cent.

The pathology of interstitial cystitis essentially is pan-mural inflammation, involving the entire vesical wall. Gross inspection of a typical Hunner ulcer resembles a pink, puckered, contracted ridge, on the summit of which is a linear, so-called "ulcer," frequently covered with a faint white exudate. Location is characteristic as it occurs on the movable portion of the bladder. Long duration of clock-like frequency occurring day and night is a characteristic symptom. If the bladder is not emptied immediately, severe urgency and pain will follow.

The diagnosis is made from the history, presence of reduced bladder capacity and by demonstration of the ulcer by cystoscopy. The urine is usually clear. Treatment constitutes one of the most difficult procedures of urology. The ineffectiveness of any one course is tested by the numerous methods being employed. Currently, hydrostatic distention with fulguration of the lesion with silver nitrate or high frequency coagulating units often affords temporary relief. Recurrence of symptoms is unfortunately frequent, the interval period of comfort varying from 3 months to 1 year, when the procedure must be repeated. Surgical approach is not indicated except in a few cases where bilateral ureterosigmoidostomy becomes a necessity.

HYPERPARATHYROIDISM

Robert W. Schneider, M.D.

Kidney damage in hyperparathyroidism may be of two types: nephrocalcinosis and nephrolithiasis. Kidney damage is more common in hyperparathyroidism than is skeletal involvement. Not over 5 per cent of all kidney stones is caused by hyperparathyroidism. A fatal disease when unrecognized, hyperparathyroidism should not be overlooked merely because it is a rare cause of stones particularly since it is curable. Certain cardinal symptoms and signs of hyperparathyroidism will aid in recognizing at least some of the kidney stones that are caused by hyperparathyroidism. Outstanding symptoms are polydipsia, polyuria, nocturia, muscular weakness, dysphagia, anorexia, nausea, vomiting, constipation, skeletal pain, tumor, deformity or fracture.

Signs in hyperparathyroidism are meager and usually absent. Loose teeth, epulides, muscular flaccidity and hyporeflexia are significant. Only 10 per cent of all parathyroid tumors are clinically palpable. Skeletal changes occur in only 30 per cent of all cases. The alkaline phosphatase is elevated only when the skeleton is involved.

Laboratory:

1. Persistently low blood phosphorus.
2. Sulkowitch test (office procedure). Many causes for a positive Sulkowitch test.
3. Normal blood phosphorus in the presence of a reduced urea clearance.
4. Elevated blood calcium which may be intermittently normal. Many other diseases are associated with a high blood calcium and kidney stones.
5. Total blood protein may aid in evaluating the level of ionic calcium.
6. Urea clearance (not always essential; may explain the absence of a low blood phosphorus).
7. X-ray of the teeth for destruction of lamina dura.
8. X-rays of long bones.

9. Alkaline phosphatase (of limited value).
10. Low calcium diet (only of value to aid in preparation of patient for 24 hour urine calcium determination in borderline cases).

The recognition of one case of hyperparathyroidism is ample reward for the effort involved.

DIAGNOSIS AND TREATMENT OF URINARY CALCULI

Charles C. Higgins, M.D.

It is generally conceded that there is no single factor responsible for the formation of all renal calculi. Preoperative investigation should include the following:

1. Infection
   a. Focal infection
   b. Local infection
      (1) Gram stain
      (2) Culture
      (3) Urea splitting
2. Hyperparathyroidism
3. Metabolic diseases
   a. Gout
   b. Oxaluria
   c. Cystinuria
   d. Xanthinuria
   e. Phosphaturia
      (1) Temporary
      (2) Permanent infected
      (3) Permanent noninfected
4. Excess of crystalloids in the urine
5. Hydrotrophic substances and colloids
6. Vitamin A deficiency
7. Vitamin B deficiency
8. Stasis

Errors in the diagnosis are sins of omission. With refinements in diagnostic procedures, i.e., intravenous urography, retrograde pyelograms with contrast media or air, and lateral pyelograms, a diagnosis always can be established. Conservative surgical procedures should be employed. Since the introduction of the newer chemotherapeutic agents, infections involving the kidney, which in the past failed to respond to treatment, now may be readily eradicated. Extensive nephrotomies may be employed to remove stag-horn stones from the kidney, and in other instances a heminephrectomy may be advisable. The majority of calculi confined to the pelvis of the kidney may be removed through the simple linear incision, pyelotomie elargie, or the inferior pyelotomy. incision. The postoperative management consists of:

1. Chemical analysis of the stone
2. Abundance of water
3. Elimination of stasis
4. Eradication of infection
   a. Local
   b. Focal
5. Correction of metabolic errors

6. Treatment of hyperparathyroidism if present
7. Correction of vitamin A deficiency
8. Correction of vitamin B deficiency
9. Dietary adjustment

The diet to be employed is determined by the chemical constituents of the stone and the pH of the urine from the kidney that harbored the calculus. It serves to control the pH of the urine maintaining the crystalloids in complete solution and minimizes the excretion of crystalloids in the urine. In general it has been stated that the incidence of recurrent stone formation following the removal of a calculus from the kidney varied from 10 to 40 per cent. Prior to the use of dietary management our incidence of recurrent stone formation was 16.9 per cent. Since utilizing the diet in conjunction with the other therapeutic procedures employed in the past, the incidence of recurrence has been reduced to 2.9 per cent.

The dietary management is also used for dissolution of renal calculi in a selected group of patients, obviating the necessity of surgical intervention. Patients who have passed a calculus spontaneously or in whom a calculus has been removed from the ureter by manipulative procedures should be placed on the diet to prevent further stone formation. The patients are instructed how to test and record the pH of the urine daily. These reports are presented to their physicians at monthly intervals. If the pH is not being maintained at the correct level, modifications of the constituents of the diet are essential. Complete cooperation among the physician, surgeon, and the patient is required to maintain a low morbidity and prevent recurrent renal calculus formation.

VESICAL NECK OBSTRUCTION IN WOMEN AND CHILDREN

William J. Engel, M.D.

Obstruction of the vesical neck is frequently unrecognized in women. The symptoms, which are similar to those occurring in men, consist of slowing of the urinary stream with hesitancy in starting, frequency and nocturia, and burning and urgency if pyuria is present. Such obstructions are most common during the fourth and fifth decades. Diagnosis is based on the history, repeated checks of the residual urine, cystoscopic findings which include increased coarse trabeculation, (sometimes deep saccules or small diverticula) hypertrophy of trigone, elevation of the floor of the vesical neck similar to that seen in contracture and median bar in men and depression of the bladder behind vesical neck. Atonic dilated ureteral orifices are seen in long-standing cases, and the cystogram may show a sacculated bladder and in late cases bilateral ureteral reflux. Several theories of causation have been proposed: 1. Fibrous contracture resulting from chronic inflammation, accepted by most; 2. Female prostate—glandular elemer ts; 3. Congenital vesical neck contracture, probable factor in some of younger cases. The condition must be differentiated from neurogenic vesical dysfunction associated with spina bifida, multiple sclerosis, lesions of cauda equina, and cord changes associated with such diseases as diabetes and pernicious anemia. Excised tissue generally shows fibrosis, chronic inflammation, and occasionally glandular elements. Treatment includes urethral dilations, which are usually unsuccessful and transurethral resection of the vesical neck, which is preferred. This procedure requires careful resection. A resection of the lower 180 degrees or less is generally adequate, and it is better to take too little and repeat than too much and regret.

In children vesical neck obstruction is seen predominantly in boys. Several types are encountered: 1. Vesical neck contractures; 2. Posterior urethral valves; 3. Imper-

forate urethra. The most common symptoms and signs consist of frequency of urination and enuresis. The bladder may be palpable. Persistent pyuria and recurrent pyelitis are common. Anemia, weakness, and failure to develop properly are often associated. The diagnosis is made on the basis of the presence of residual urine, intravenous pyelogram, and cystourethroscopic examination. Early recognition and correction prevent renal damage. The obstruction can be relieved either by endoscopic resection or occasionally by suprapubic cystostomy. Too often the results are unsatisfactory because the problem has been recognized too late. It is frequently necessary to control the chronic infection with antibiotics and the sulfa drugs.

AZOTEMIA PRECIPITATED BY SODIUM DEPLETION

Robert D. Taylor, M.D.

The recent recognition of the value of sodium restriction in the treatment of heart failure and hypertensive disease, combined with the more generous use of mercurial diuretics, has increased the frequency with which azotemia is observed as the result of sodium depletion. Although the syndrome can be induced in normal people, it occurs much more readily in patients with some pre-existing impairment of renal function.

Symptoms of the condition are: drowsiness, weakness and lethargy; anorexia, nausea and sometimes vomiting. There is progressive oliguria, weight gain and edema formation. The laboratory findings are progressive azotemia and decrease in urinary chlorides and sodium values. There is evidence of dilution of body electrolytes. The plasma chlorides and total base values are sharply reduced.

Explanation for the occurrence of renal deterioration and azotemia because of sodium depletion is not known. However, unless the electrolyte deficit is corrected, uremia will be progressive and death may occur.

Treatment consists in administering enough sodium chloride so that the extracellular water can be restored to its normal tonicity. This can be done only by supplying NaCl in excess. If it cannot be taken orally, hypertonic solutions by vein are necessary to effect diuresis and normal blood electrolyte values.

PRODUCTION OF GASTROINTESTINAL SYMPTOMS BY GENITOURINARY DISEASE

Eugene F. Poutasse, M.D.

The presenting and sometimes only symptoms in about one-fourth of all upper urinary tract disease may be gastrointestinal in nature. Chief among these are nausea and vomiting, pain in any of the four quadrants of the abdomen, and constipation or diarrhea.

The reason for the confusing symptomatology is the analogous autonomic nervous system innervation of the kidneys and ureter with that of the gastrointestinal tract through the splanchnic nerves, celiac and aortic ganglia.

A stone lying in the renal pelvis or at any point along the ureter frequently gives typical symptoms of a gastrointestinal disease such as appendicitis, gallbladder disease, or intestinal obstruction. Other lesions often producing gastrointestinal symptoms are hydronephrosis, renal tumor, uremia, acute urinary infections, seminal vesiculitis or anomalies of the urinary tract.

A careful history and physical examination usually provides some clue pointing to the urinary tract in these cases. The urine should always be examined and in women it

must be a catheterized specimen. Appropriate studies must then be made to ascertain the diagnosis. Many patients are subjected to unnecessary exploratory operations for inadequately studied urinary tract disease causing gastrointestinal symptoms.

PROSTATISM AND PROSTATIC CARCINOMA

Charles C. Higgins, M.D.

Many men consider symptoms due to prostatic hyperplasia as indicative of advancing years and accordingly fail to secure medical attention. The patient may first notice some hesitancy, frequency, and slowness and lack of force of the urinary stream and subsequently nocturia of increasing frequency. An attack of complete retention may follow exposure to the cold or overindulgence in alcoholic beverages. Symptoms of prostatic obstruction are not proportional to the degree of enlargement of the gland. Thus a large gland that does not encroach upon the vesical outlet does not produce obstructive symptoms as pronounced as those caused by a small gland intruding into the vesical orifice.

A complete physical examination is essential, as in the last 600 patients I have operated on for prostatic obstruction cardiovascular complications were present in 210 and other complicating systemic diseases in 78 patients. Instrumentation may prove a dangerous procedure in the elderly individual with a large residual urine for a long time because it may provoke an exacerbation of infection. Determination of renal function (blood chemistry studies) and an intravenous urogram are secured routinely. The urogram supplies information regarding renal function and determines whether dilation of the ureters with coexisting hydronephrosis is present.

No one surgical procedure, in my opinion, is suitable to relieve all cases of prostatic obstruction. If preliminary drainage is required for more than a few days, I prefer to perform a trocar puncture for drainage rather than a urethral catheter. The former prevents the development of an urethritis and minimizes the incidence of epididymitis.

Approximately 70 to 75 per cent of the cases can be treated by a transurethral prostatectomy. When the gland is large and intravesical intrusion pronounced, I prefer suprapubic prostatectomy. By careful selection of cases, excellent results may be secured with both procedures. In a series of 1000 patients with prostatism I operated upon and reviewed a few years ago, the operative mortality was 2.5 per cent.

Carcinoma of the prostate still presents a baffling problem and a challenge to the urologist. The symptoms may simulate those of prostatic hyperplasia, i.e. frequency, difficulty, lack of force of the stream, and nocturia. Early in the course of the disease the patient may be free of symptoms. Carcinoma of the prostate usually has been present for 2 to 4 years before the diagnosis is established. The diagnosis is based upon rectal palpation of the prostate, laboratory data, and roentgenography.

Even if the gland is not stony hard, extensive induration and fixation, especially if the seminal vesicles are involved, suggest carcinoma of the prostate. A small nodule in the presence of hyperplasia of the prostate may be overlooked.

Acid and alkaline phosphatase determinations should be made on each patient. In the absence of metastasis as elicited by roentgenograms, the acid phosphatase was normal in 72 per cent of the cases. The alkaline phosphatase was normal in 70 per cent. In the presence of metastasis the acid phosphatase was normal in 38 per cent and the alkaline phosphatase in 16 per cent. Roentgenograms of the lungs, spine, and pelvis are advisable to determine the presence or absence of metastasis.

Early diagnosis is essential. If a nodule is palpable in the prostate of a patient 50 years of age or over, I believe perineal exploration is imperative. If the nodule is an

adenoma, it may be removed and the incision closed, and the patient leaves the hospital in a few days. If, however, the nodule is malignant, a radical perineal prostatectomy should be performed. At this stage of the disease a cure probably can be secured by this operation. Therefore, for early carcinoma of the prostate, when the malignancy is confined to the gland, a radical perineal prostatectomy is the procedure of choice.

Unfortunately, at the time the diagnosis is established the disease usually has extended beyond the confines of the gland, and endocrine therapy is necessary. Three types of treatment may be instituted:

1. Orchiectomy
2. Orchiectomy plus stilbestrol
3. Stilbestrol

In most instances I prefer stilbestrol alone. The dosage of the drug varies and I usually begin with a dosage of 4 mg. daily. There is accumulating evidence that in the absence of metastasis orchiectomy plus stilbestrol is the preferred treatment. During the past year I have performed orchiectomies in only 7 patients. It must be recalled that endocrine therapy is not a cure, while radical surgery early in the course of the disease may offer hope for a cure by complete extirpation of the lesion.

MANAGEMENT OF ACUTE ANURIA

A. C. Corcoran, M.D.

Management of acute anuria is directed towards supporting the chemical structure of the body until renal function is restored. A second aim is vicarious excretion.

Support is based on giving no more fluid or electrolyte than the patient can excrete, while providing a high caloric, protein-free diet. Control of infection is essential.

Vicarious excretion is accomplished by peritoneal or blood dialysis or by intestinal perfusion. All these procedures require a maximum of chemical control and may do, at times, more harm than good. Especially in anuria must we recall the old axiom "nihil nocere."

PANEL DISCUSSION (Abbreviated)

(Drs. Taylor, Leiter, Higgins, Corcoran, and Poutasse)

Dr. Jordan: Here is the first question. In view of the dramatic results in treatment of calculi medically, what would be your indication for nephrolithotomy?

Dr. Higgins: In the majority of instances, when there is a stone in the ureteropelvic junction that is obstructive in nature, destroying renal parenchyma, producing stasis, surgical intervention is advisable. I demonstrated some cases yesterday in which stones formed both in alkaline and acid urine were completely dissolved by dietary means. I do not wish to imply that this can be secured routinely. There is still a missing link in the dietary treatment of calculous disease. The role of diet at the present time is primarily to prevent recurring stones following operation. Frequency of recurrence before we used diet in conjunction with other procedures was 16.9 per cent. Our recurrence rate for stones at present is 2.9 per cent. The patients now forming recurring stones are those in whom we cannot control the pH of the urine due to the presence of a urea-splitting infection. If the stone lies in a calyx and is not obstructive, I think one is justified in attempting dissolution by dietary means. Stones in the kidney pelvis, stones

in the urethrocystic junction I believe are definitely surgical problems at the present time.

Dr. Jordan: Is the serum protein necessary in blood calcium and phosphorus determinations? Is that question clear?

Dr. Leiter: I suppose it involves the question of the relationship between the serum calcium level on the one hand and the phosphate and plasma protein on the other. Essentially the serum calcium concentration exists in two forms, about half in ionized form and about half in some sort of protein-bound form. Now the fraction which is bound to protein will, of course, be determined quantitatively by the amount of protein in the plasma; in conditions with low serum protein, that portion of the serum calcium will be diminished. On the other hand, the ionized calcium may still be perfectly normal and there will be no signs of tetany. Serum phosphate retention will cause a reduction of the ionized serum calcium. That is one reason why in hypoparathyroidism due to the removal of the parathyroids one finds elevated serum phosphate and decreased serum calcium. In certain conditions associated with hypocalcemia certain bone tumors—multiple myelomas—and so on, high levels of serum calcium may develop without elevation of the plasma proteins and without any remarkable reduction of phosphate in the serum because phosphate is coming into the bones along with calcium. There apparently is some sort of special protein fraction that has an unusual binding ability for calcium which comes into the serum presumably from the bones as well.

Dr. Jordan: Is increased acid phosphatase pathognomonic of metastatic prostatic carcinoma?

Dr. Higgins: In a vast majority of cases an increase in a serum acid phosphatase is extremely suggestive of metastatic carcinoma. A normal acid phosphatase does not mean that metastases are not present because we know that a certain group of the carcinomatoid cells undergo anaplasia and lose their power of secreting the phosphatase.

Dr. Jordan: A corollary question is: What acid and alkaline phosphatase determinations do you use and what levels do you consider abnormal?

Dr. Higgins: We use the Bodansky method, 0.1 to 1.0 acid phosphatase and 1.5 to 4.0 alkaline phosphatase.

Dr. Jordan: Dr. Taylor, here is a question that hasn't come up in this course but I know you can answer it. Please discuss lithium salt poisoning.

Dr. Taylor: Lithium intoxication was first described as far as we know in 1913 by a Dr. S. A. Cleaveland, who lives here in Cleveland. He induced it in himself while he was a student at Western Reserve University. He was on an experimental diet which was low in sodium designed to find out how lithium was metabolized in the body. He took about 5 grams of lithium before he went to a football game and in the middle of the game he began to see 33 players instead of 22, became rather foggy about where he was, and had trouble finding his way home. He became drowsy and developed some muscular tremors. He reported this experience in the Journal of the American Medical Association. All the patients we have observed and reported were on a low sodium diet. Apparently lithium is metabolized in the place of sodium in the body when there is a deficit of sodium present. When lithium is metabolized in the place of sodium, cerebral irritation occurs and it gives a unique picture of a severe hyperirritability of all of the reflexes and of all of the muscles of the body. There is a tremor that is gross and uncontrollable. The patients do not have azotemia or hypochloremia. They do not have decreased chlorides in their urine, and they do not have the oliguria that is associated with hyponatremia. In rats which are given a diet adequate in sodium, lithium produces no symptoms but if the lithium is given to rats fed on a low sodium diet, the same syndrome

appears in them as in human beings. It seems clear that lithium intoxication doesn't occur unless patients are on a low sodium diet.

Dr. Jordan: Would you like to add to that, Dr. Leiter?

Dr. Leiter: In our use of lithium at the Montefiore Hospital we were fortunate in not observing any of the gross manifestations of toxicity. After they were described in the literature, we went back and looked over our records and did not find any evidence of the severe forms of intoxication. Perhaps the reason was that we were careful not to use lithium salts in the old patients with arteriosclerotic heart disease, cerebral arteriosclerosis, or renal insufficiency. Most of our cases treated were younger persons with rheumatic heart disease. The amount of lithium was small. We did not add it to the food in the cooking, not in the hospital certainly, chiefly I think because we didn't want to have chloride in the urine which would confuse our chloride determinations. Only a few were allowed to take it at home.

Dr. Jordan: You don't disagree with Dr. Taylor?

Dr. Leiter: No, I don't disagree with his conclusions at all. It is not surprising that low serum sodium has been associated with lithium intoxication since the condition for which lithium is usually given, namely congestive heart failure, and its treatment with a low salt diet is also likely of itself to produce a low serum sodium.

Dr. Jordan: What are the indications for surgery in tuberculosis of the genitourinary tract and when should that surgery be done?

Dr. Higgins: I suppose the question is aimed primarily at renal tuberculosis. Renal tuberculosis is a local manifestation of the general disease. Therefore, if the patient has active pulmonary tuberculosis, has fever which may be due to an active renal tuberculosis, certainly immediate surgery is contraindicated due to the dangers of a miliary tuberculosis. Sanatorium treatment is necessary. If the patient does not have fever, he may be treated on an ambulatory basis and given streptomycin. I personally prefer to give the streptomycin for a period of 2 weeks prior to operation, if the patient has a normal temperature.

Dr. Jordan: What is the present attitude about orthostatic albuminuria?

Dr. Leiter: It is an optimistic one. Making certain that it is only harmless proteinuria is important. The urine should be obtained during recumbency without lordosis. If such a urine is free from albumin and if there is no history of recent or previous acute nephritis or recent acute infection, then the attitude toward posture proteinuria should be optimistic. An intravenous pyelogram might also be done to make sure that there is no vascular anomaly affecting the ureteropelvic junction on one side producing proteinuria.

Dr. Jordan: Dr. Taylor, do you want to make any comment?

Dr. Taylor: What I'm thinking about is not really orthostatic albuminuria. There are some patients who have acute glomerulonephritis and recover from it completely but continue to have an abnormal degree of proteinuria which is not significant of progressive, degenerative renal disease. When there is a moderate amount of proteinuria even up to 0.4 or a half a gram for 24 hours with no abnormal cellular elements in the urine and no decrease in tubular function or glomerular function for 2 or 3 years, I think one can assume that this is a residue of glomerulonephritis and may be present all the patient's life. It need not contraindicate buying insurance, getting married, or having children, but it does occur and it sometimes leads to misunderstanding and mistaken prognosis.

Dr. Jordan: Dr. Poutasse, there are five questions which deal with some of the subjects you discussed. (1) Which is the drug best suited for the various urinary infections? (2) To establish the type of infecting organism is it necessary in men to obtain

a catheterized specimen or is it permissible after cleansing of the glans to have the patient void into a sterile test tube which is being sent to the laboratory for culture? (3) Is there any rationale in using an unabsorbable sulfa drug in repeated recurrences of coli urinary infections? (4) The sensitivity test of the various antibiotics was mentioned. Would you please give in more detail the technic of the test? (5) Is pyelitis mostly blood-borne or ascending (especially in pregnancy)?

Dr. Poutasse: In answer to the second question, a clean voided specimen in a man is often a satisfactory way of obtaining culture. Perhaps the best way is passing a catheter, but this is not always feasible. There is no one urinary antiseptic that is effective against all organisms. As for the first question, there is reason to believe that chloromycetin and aureomycin may act on most urinary infections. However, there are other useful drugs and indications, of course, dependent upon the organism that is infecting the urinary tract. To the third question I should say that if an unabsorbable sulfa preparation proved ineffective, I would certainly switch to something else such as the more expensive drugs—aureomycin and chloromycetin; for a long period of treatment, mandelamine or mandelic acid may prove fairly effective.

The technic for sensitivity testing varies with different laboratories. The procedure that we use here is to take a culture plate and smear the entire surface with the organism, then place on it the little filter papers which have been wetted with the known strength of each drug. Twenty-four hours later the diameter of the clear area around the filter paper gives an index of the antibacterial activity of the agent.

Dr. Jordan: Then the last question: Pyelitis—is it mostly blood-borne or ascending (especially in pregnancy)?

Dr. Poutasse: It is difficult to answer this question. It is usually believed that infection gets to the kidney and urinary tract either through the blood stream or the lymphatics. Sometimes there can be an ascending infection, particularly when there is obstruction at the lower portion of the urinary tract.

Dr. Taylor: I would like to put a word in on that. I don't think there is any such thing as pyelitis exclusively; I think it is always pyelonephritis or nephropyelitis. I don't see how it is possible for a kidney pelvis to be inflamed without the whole kidney being involved with it. I think pyelitis is a term that should be completely discarded. Unless there is definite evidence of obstruction of the free flow of urine such as prostatism, strictures, or tumors, one may assume that there are constant showers of bacteria which come from teeth, tonsils, and the intestinal tract into the blood. There is little evidence to back up lymphatic origin of such infections. It is pyelonephritis or nephropyelitis, whichever you want to call it.

Dr. Leiter: I agree with Dr. Taylor in regard to doing away with the term pyelitis. It certainly should be pyelonephritis. If we learn to think of pyelonephritis, we will recognize these cases much earlier and shall see fewer of the neglected or so-called latent and chronic types of pyelonephritis.

Dr. Higgins: I agree with Dr. Taylor. The modern concept, of course, of pyelitis is that pyelitis per se is an extremely rare clinical entity. It is usually a pyelonephritis. It is always preferable, if possible, to secure a catheterized specimen from the male. One must remember that there are always nonpathogenic organisms in the anterior urethra. If conditions are such that one cannot secure a catheterized specimen, it does not suffice merely to wash the glans. The patient must void, wash out the anterior urethra, and the second portion of the urine must be utilized for the culture. There is one other feature in the treatment of urinary tract infections. In the presence of stasis one must determine if the organism possesses the power of splitting urea because if it does ammonium chlor-

ide (which is the common acidifying agent used) is contraindicated. Giving ammonium chloride aids in the formation of a stone in the kidney in the presence of stasis.

Dr. Jordan: What is alphalin?

Dr. Taylor: Alphalin is a proprietary drug marketed by Lilly Laboratories. It is their brand of vitamin A. We have used it because, whether accidentally or not, we observed that it increased renal function in hypertensive persons and persons with degenerative renal disease. The effect is not due to the vitamin A itself because crystalline vitamin A doesn't have it. Something in the fish oils which contain vitamin A enhances renal blood flow, filtration rate, and tubular secretory capacity—certainly patients feel better and it's easier to take care of them over a long term when they are getting large amounts of this fish oil. Have you used any, Dr. Leiter?

Dr. Leiter: No, I haven't.

Dr. Jordan: Is there an alternative to periodic massage of a prostate in a young man who—or which—presents an expressable bulge on rectal palpation and which, when not massaged, about monthly produces symptoms of urethritis?

Dr. Higgins: About 35 per cent of men past the age of 37 have microscopic evidence of a so-called chronic prostatitis. Now I do not believe that we are justified in massaging the prostate of such a man unless there is evidence that the prostate is acting as a focus of infection. The prostatic massage merely facilitates drainage from the obstructed ducts of the prostate gland. If the man does have a persistent urethritis, I think probably an occasional prostatic massage is indicated. The primary disease may not be the prostate gland. If patients who have a chronic prostatitis do not respond to prostatic massage, a couple of injections of penicillin sometimes help. Always one must examine the teeth by x-ray to rule out the possibility of a dental root abscess serving as the initial focus of infection.

Dr. Jordan: In your use of low sodium diets, do you follow urine chloride excretion, and if so, by what method?

Dr. Corcoran: We actually follow urine sodium excretion. The correlation at low levels of sodium chloride is not too good since chloride at its best is a rough measure of the degree of sodium restriction. Don't you agree, Dr. Leiter?

Dr. Leiter: Yes, and certainly if you are giving ammonium chloride before mercurial diuretics, you can't follow the excretion at all.

Dr. Jordan: When the ureter is hopelessly involved by rectosigmoid carcinoma and the tumor is removed, how is the remaining segment of ureter and corresponding kidney dealt with?

Dr. Higgins: I suppose the question infers that at the time of operation it is necessary to remove a segment of the ureter. If this is a small segment, I would not hesitate to pass one end of the catheter up to the kidney pelvis, the other end into the bladder, and then bring it to the outside by means of a cystoscope. This leaves the possibility of the patient developing a stricture at a later date. There is one other possibility—anastomosing one ureter to the ureter on the opposite side which I reported some time ago. Finally if one has a normal kidney on the side of the lesion, an autonephrectomy can be produced in that kidney merely by ligation of the ureter. This would be satisfactory except that one loses the function of the kidney. The kidney undergoes—first, a slight hydronephrosis, later atrophy. Surgical removal is not necessary in the absence of infection.

Dr. Jordan: Here is a long question. In our Urological Department we do a great many cystoscopic examinations under anesthesia. Apparently normal persons show definite delay in excretion of both indigo carmine and phenolsulfonphthalein under

anesthesia. In other words, the normal excretion time of 3 to 5 minutes, following intravenous administration of the dye, is repeatedly delayed from 6 to 8 minutes. Please discuss the effect of anesthesia upon kidney.

Dr. Corcoran: It depends on the anesthetic. The delay time is contingent on the rate of urine flow. There is a certain amount of urine in the kidney pelvis and ureter and it must flow on before the dye appears. The appearance time can be as rapid as 1 or 1½ minutes but with a slow rate of flow the time increases. Ether anesthesia, for instance, causes an oliguria, and deep anesthesia of any kind is associated with oliguria. This results in a delay in appearance time.

Dr. Higgins: I agree 100 per cent. In the ordinary cystoscopic examination, however, when the catheter to the renal pelvis is placed without an x-ray film there is no way that one can ascertain whether or not the catheter is in the renal pelvis or in one of the upper calyces. Obviously, if it is in an upper calyx, the drainage is not comparable to that in the opposite kidney if the catheter is in the renal pelvis. The other mistake that is frequently made with the phenolsulfonphthalein test is to rely entirely on the amount of excretion from the kidneys. Unless the specimen is taken from the bladder and the phenolsulfonphthalein content of the urine in the bladder determined, that is the urine is passed around the catheter down to the bladder, the test is not accurate.

Dr. Jordan: Is there any scientific evidence to show that renal function or renal pathology is influenced favorably by so-called kidney substances commercially known as nephrotin?

Dr. Taylor: No.

Dr. Jordan: Do you consider the complications of retropubic prostatectomy any more formidable than those of radical perineal prostatectomy, e.g. the various types of fistulas following this latter procedure?

Dr. Higgins: Definitely. I think for the majority of surgeons doing work on prostatic hypertrophy, suprapubic prostatectomy is preferable. A transurethral resection is extremely technical. If it is done correctly, one must extend the operation proximal to the verumontanum so as to be in close proximity to the external sphincter. The ordinary perineal prostatectomy is a completely anatomic approach. There should not be the complications of fistula. The same applies to the radical perineal prostatectomy. Now, of course, one cannot compare the results of retropubic prostatectomy to the radical perineal prostatectomy for carcinoma of the prostate. Two entirely different lesions are involved. As I stated yesterday, the incidence of osteitis pubis is so high that at present I have discontinued the operation until we can definitely determine the causative factors responsible for this complication.

Dr. Jordan: Please give the pathologic physiology of nocturia. Is there an associated diurnal polyuria?

Dr. Leiter: The nocturia, of course, can result from any disturbance from the cerebral cortex on down to the end of the urethra, I suppose, since it involves partly the question of frequency of emptying of the bladder. From the purely medical point of view we usually look upon nocturia as a lag in the excretion of urine during the daytime followed by an increase of excretion during the night and, therefore, also associated with larger urine volumes during the night. That would lead one to think of all conditions in which the excretion of water is delayed, assuming that the individual ingests water during the daytime. Therefore, almost any type of chronic renal disease, almost any type of secretory failure, or conditions such as diabetes insipidus where there is a continuous and large flow of urine with the associated thirst, would be likely to produce nocturia. Dr. Higgins will probably mention some local renal factors which may be important. What was the rest of it?

Dr. Jordan: Is there an associated diurnal polyuria?

Dr. Leiter: As to whether the total 24 hour urine volume is also decreased, or rather the frequency of urination during the day, that will vary with the etiologic factors. If it is something in the way of irritation in the urinary tract, inflammation and what-not, of course there will be an associated diurnal polyuria. If it is chronic nephritis with renal impairment or cardiac insufficiency or any condition associated with edema or tendency to it, there will be less urine put out during the day and the total 24 hour urine volume may not be increased. In fact, it may even be greatly reduced. The most important cause, I think, for nocturia is too much drinking of water before going to bed.

Dr. Higgins: The nocturia which perturbs the urologist is that which is associated with prostatic hypertrophy. Since the back pressure is transmitted up the ureter and the kidney pelvis, the primary impairment of function is tubular in origin, and that is one of the reasons for nocturia. In addition to this, as Dr. Leiter stated, such patients have had too much water or overindulged in alcoholic beverages.

Dr. Jordan: Dr. Corcoran, do you have anything to add?

Dr. Corcoran: No, just that Dr. Taylor has emphasized something that we commonly lose sight of—that nocturia may be one of the earliest evidences of congestive heart failure. Frequently, because the presenting symptom is nocturia, the heart is not given proper attention and the kidneys receive a lot more than they deserve.

Dr. Jordan: Dr. Higgins, what is the role of introduction of a sclerosing agent following aspiration of a solitary renal cyst?

Dr. Higgins: I have never introduced a sclerosing solution following aspiration of a solitary cyst of the kidney. I have on several occasions aspirated the fluid and as yet I have not seen a recurrence. Why this is I do not know. If the fluid is crystalline clear, that is all that is necessary. If, however, the fluid is hemorrhagic in nature, one must suspect a papillary tumor in the cyst and exploration is advisable. The cysts that I have aspirated I have not seen refill.

Dr. Leiter: I should like to ask Dr. Higgins whether he aspirates cysts in polycystic kidneys and whether he cauterizes them or does anything else besides aspiration.

Dr. Higgins: Some cases we have aspirated by open operation—as a matter of fact, cut them right open. Goldstein of Baltimore recommends marsupialization—that is, not to the skin but underneath the skin, so that he can aspirate them at any time he wishes. I think it is a good procedure in failing renal function in polycystic kidney.

Dr. Jordan: What happens in the kidney when respiratory acidosis or alkalosis exists?

Dr. Corcoran: When respiratory alkalosis exists, there is some polyuria and an increase in urinary bicarbonate. I think it is merely an osmotic diuresis. In respiratory acidosis I know nothing of what happens except that there is usually a good deal of associated oxygen lack and consequently oliguria. Can you answer that question, Dr. Leiter?

Dr. Leiter: I think in respiratory alkalosis there is available a temporary excess of sodium to be excreted, and it is if the kidneys are functioning normally. I suppose in emphysema with severe retention of carbon dioxide there would be a reason for disposing of more chloride in order to balance the sum of carbon dioxide and chloride in the blood.

Dr. Jordan: Here is a case question. A boy of 13 shows 4+ albumin during the day and only a faint trace on arising. He shows 3 to 4 white blood cells per high power field not centrifuged. Please discuss possibilities.

Dr. Taylor: The implication is that orthostatic albuminuria has to be considered, but if the 4+ albuminuria means the 6 to 10 grams per 24 hours it should, that is a

great amount of proteinuria for an orthostatic problem. I would think that this boy should be investigated for a chronic renal disease; he is 13; he certainly is in the age group when one could have a glomerulonephritis of an acute or chronic variety, and certainly his filtration rate should be measured promptly by urea clearance or any other methods available. Surely the Addis examination should be performed which will give an estimate of tubular function, if he has no edema, and it will also tell what this 4+ albuminuria means. Unfortunately, one often sees 4+ albuminuria recorded when it means less than a gram for 24 hours, and some technicians' and even some physicians' estimates of 4+ albuminuria are not accurate. A count of the sediment certainly has to be made to see whether or not these red cells, 3 to 4, are normal or whether there is hematuria. My guess is that a boy who puts out 6 grams or 10 grams of protein in a period of 24 hours, and has red cells, has a glomerulonephritis in either the acute, or healing, or chronic phase.

Dr. Higgins: This question states that he shows 4+ albuminuria during the day but only a faint trace on arising.

Dr. Taylor: I don't believe the laboratory.

Dr. Corcoran: Any proteinuria is orthostatic in a degree. A chronic nephritic proteinuria is partly orthostatic.

Dr. Taylor: We don't know anything about the concentration of the urine—we don't know anything. But anybody who has 4+ albuminuria and red cells in the urine has to be considered to have chronic nephritis until proven otherwise—or glomerulonephritis—until proven otherwise.

Dr. Leiter: I don't see the word "red cells" mentioned here. It says white cells.

Dr. Taylor: Oh, it did. I thought they were red cells.

Dr. Leiter: If there were red cells in the urine, I would certainly agree with Dr. Taylor that glomerulonephritis should be excluded. Regardless of what there is in the urine any youngster with a 4+ albuminuria diurnally (unless it can be shown during the day to be subject to complete remission with change of posture) should be investigated for the diseases mentioned and certainly should have an intravenous pyelogram to exclude some urologic anomaly.

Dr. Jordan: Can you tell us about the surgical treatment of hypospadias in children?

Dr. Higgins: Hypospadias is a plastic surgical procedure. One cannot perform a plastic operation on the penis in the absence of erection and then have the patient develop an erection and have the sutures hold. Therefore, the patients should all receive stilbestrol preoperatively until they do not have a morning erection. The plastic procedures are difficult—or they have been in the past, and I finally resorted to using the Ombredanne's technic for all patients. There is a new operation that is now out which I think is the finest technic that I have employed and certainly our results are gratifying. I would have to draw this on the blackboard, and if the doctor who asked the question would come up after we are through, I would be glad to show him the technics.

Dr. Jordan: What are the lesions in the kidney referred to as sulfa intoxication other than those secondary to sulfa crystal urea?

Dr. Leiter: The anatomic lesions in the kidney apart from the actual presence of crystals in the tubules or anywhere in the urinary tract are far more important than the presence of crystals. Granulomas may form about tubules in which I suppose crystals have precipitated at one time, or about degenerating tubular epithelium. These granulomas may be widespread and ultimately lead to fibrosis and uremia or they may lead to acute fatal uremia. In addition to that, there may be lesions which are absolutely

typical for so-called periarteritis nodosa or allergic arteritis with necrosis and inflammatory reaction in and about the smaller arteries which in themselves are a serious form of damage to the kidney.

Dr. Taylor: There is another allergic reaction which occurs in these persons. I think Dr. Castleman in Boston was one of the first to recognize it. It is not unlike the syndrome that occurs in lower nephron nephrosis. There is an allergic response in which the tubular cells just degenerate. Some recover, but the majority die.

Dr. Corcoran: I was going to ask Dr. Leiter if he has seen many instances of sulfa intoxication which resulted in a permanent, prolonged renal disease.

Dr. Leiter: I have seen only one instance in which progressive renal impairment occurred over a period of months. This was in the early days of the use of sulfapyridine in the treatment of pneumonia. At that autopsy the kidney was full of granulomas—enough of them so that renal tissue was effectively destroyed.

Dr. Jordan: Is the Fishberg modification of the Volhard and Farr concentration test sufficient as an office screening test for the presence of glomerulonephritis and nephrosclerosis?

Dr. Taylor: I don't think so. Back in 1944 and 1945 we tried to get a simplified procedure which would combine short periods of dehydration with the antidiuretic effect of pituitrin. Dr. Sodeman in New Orleans suggested that pituitrin alone as stimulus to tubular reabsorption would be enough to measure the ability to concentrate urine, but we were unable to find a substitute for the Addis test which would give equivalent results. Sometimes the results of the Fishberg test were excellent, but if a person had been consuming large quantities of fluids for a day or two beforehand, they were way off. In the summer, when perspiring a lot, we occasionally got concentrations up to 1034. The Addis test is simple; it can be done at home, is a cheap procedure and gives a tremendous amount of information.

Dr. Corcoran: There have been instances, one severe and one probably fatal reaction, from the use of pituitrin. In the latter case I think it was being used to facilitate intravenous urography. Not only is it ineffective but it may be dangerous.

Dr. Leiter: I should like to ask Dr. Corcoran whether he thinks pituitrin is as effective in patients with heart failure on the basis that there already has been an excess of antidiuretic hormone.

Dr. Corcoran: Practically everybody who has oliguria from almost any cause—lymphatic, renal, or heart failure—has already considerable amounts of antidiuretic hormone in the urine and that is probably why they don't respond much to the addition of some test material.

Dr. Jordan: Is the Clinitest method as reliable as the qualitative Benedict's test for the determination of sugar and for acetone?

Dr. Corcoran: I don't know the Clinitest method for acetone, but the Clinitest method for sugar does well if quantitative sugars are done as well.

Dr. Leiter: We have had a little difficulty with the acetone test because I think, depending upon the amount of powder used, it may be too sensitive. One may get 1+ results when there really isn't any acetone at all.

Dr. Corcoran: I might mention that Dr. Rabinovitch, my former chief in Montreal, developed a small tablet for acetone test which obviates that particular error because the tablet has a little depression into which a drop of urine is placed. Thus the ratio of urine exposure to the surface of the reagent is always constant.

Dr. Jordan: What dosage of stilbestrol do you use?

Dr. Higgins: The dosage of stilbestrol to be employed in a given case is influenced first by the presence or absence of metastases, and second by the acid and alkaline phos-

phatase studies. In the past, if metastases were not present, I started with an initial dose of 4 milligrams of stilbestrol a day—a milligram before meals and at bedtime. Now in the absence of metastases I expect to perform an orchiectomy and prescribe stilbestrol. In the presence of metastases it is necessary to use a larger dosage to control the pain and to soften the tumor, and I have no hesitancy in patients with severe pain to increase the dosage up to 25 or 30 milligrams a day. I certainly believe it is preferable to a chordotomy.

Dr. Leiter: May I ask Dr. Higgins if he has ever seen edema developing on these dosages of stilbestrol?

Dr. Higgins: I have seen it develop in patients in whom there is no apparent evidence that the tumor has extended beyond the confines of the gland. But in my experience in most of the patients who developed edema of one leg—and it is usually one leg—it is due to extension beyond the confines of the prostate.

Dr. Jordan: Why do you use urea nitrogen to the exclusion of the nonprotein nitrogen?

Dr. Leiter: It is largely because first of all it is a specific determination of a specific substance—urea. Nonprotein nitrogen, of course, includes a variety of things. Perhaps more important we do urea clearances so frequently that both blood and urine ureas are known and it is therefore not necessary to do a nonprotein nitrogen test.

Dr. Corcoran: That is the answer. I should like to ask Dr. Leiter, now that creatinine can be accurately determined by using a photoelectric colorimeter, whether it wouldn't seem advisable to shift over gradually to plasma creatinine which more closely reflects the level of filtration?

Dr. Leiter: We certainly should do creatinine studies.

Dr. Jordan: Discuss the medical treatment of idiopathic enuresis in childhood and young adults.

Dr. Higgins: As a general rule, I feel that a cystoscopic survey is not indicated. Now that is in direct contrast to the opinion of Dr. Meredith Campbell in New York, who believes he has shown a definite bulging of the sphincter which disappears as the boy or girl grows older. I believe instruction and perseverance on the part of the parents is the correct method to approach this problem.

Dr. Taylor: Dr. Higgins, how about that penile clamp you sometimes use?

Dr. Higgins: Yes, I forgot to mention it. It is an excellent method in the male. You put the small baby Cunningham clamp on the penis. During the night when his bladder is distended, he will waken, take off the clamp, and get up and void. This is an excellent method devised by Vincent O'Connor of Chicago.

Dr. Leiter: I would like to know whether Dr. O'Connor consulted the Psychoanalytic Institute in Chicago before he developed this.

Dr. Jordan: That is going over a difficult subject rapidly enough! What is the dietary management, particularly protein, in chronic glomerulonephritis?

Dr. Taylor: Some older clinicians felt that because there was protein in the urine, protein by mouth was bad. There was a time when it was thought giving protein orally would correct the hypoproteinemia which exists in this disease. As far as I am concerned, I don't think high protein diets have a great influence one way or the other. I think there should be an adequate amount of protein because most of these patients are young and they need it for growth and replacing tissues that are broken down in the body; they certainly ought to have a normal protein intake. But when azotemia appears and begins to be a problem as far as symptoms are concerned, with acidosis and anorexia and all of the things that go with it, low protein diets admittedly make these patients more comfortable, and I think make their lives last longer. If the protein intake is

reduced to approximately a half gram per kilogram per day, the management of the terminal stage of chronic nephritis becomes a much simpler problem.

Dr. Corcoran: Dr. Addis did determine that the major toxic factor in high protein diets was potassium. On the other hand Dr. Masson's rats were given diets of protein, carbohydrate, and fat which were equal and low in their potassium and other electrolyte content. The protein-fed rats died fairly quickly. Therefore, I don't think that the only factor in the toxicity of proteins is the potassium content although that is certainly considerable. We're speaking now of terminal renal failure.

Dr. Leiter: I think diets should not be changed except to alter the nutrition of the patient beneficially if renal function is above 30 or 40 per cent of normal or until it gets down to the really pre-uremic levels. I wouldn't give such patients a high protein diet or perhaps even a normal diet which contains 90 to 100 or more grams of protein, but 60, 70, and 80 grams should be harmless.

Dr. Jordan: How do you feel about doing a one stage suprapubic prostatectomy instead of a two stage?

Dr. Higgins: In most instances I would perform a one stage suprapubic prostatectomy. The lowering of mortality and morbidity, following suprapubic prostatectomy has not been accomplished by refinements in operative technic but rather by a clear understanding of secondary changes occurring in the upper urinary tract following prostatic obstruction. Whether we anticipate performing a transurethral resection or a suprapubic prostatectomy I have no hesitancy in performing the suprapubic puncture. The suprapubic puncture carries a mortality that is practically nil. The first stage prostatectomy in a patient with poor renal function carries a fairly high operative mortality. Therefore, I believe that such patients should be treated by suprapubic puncture.

Dr. Jordan: Please discuss the significance of a positive Sulkowitch test.

Dr. Taylor: A positive Sulkowitch represents a hypercalciuria. The most common condition in which it occurs is in hyperparathyroidism in which the calcium has been mobilized and excreted in the urine and leads to the formation of renal calculi which are made up predominantly of calcium.

Dr. Leiter: I think carcinoma of the breast with metastases may be a more common reason for a positive Sulkowitch.

Dr. Jordan: Discuss the status of the Streptococcus and the etiology of acute glomerulonephritis.

Dr. Taylor: It is the most common organism which causes infections in the nose and throat and such infections are the most common inciters of the antigen-antibody reaction which is responsible for glomerulonephritis. It produces an antigen to which the body produces an antibody and the reaction occurs primarily in the kidney.

Dr. Leiter: In connection with the attempts to prevent this peculiar antigen-antibody reaction which ultimately eventuates in glomerulonephritis, it should be remembered that the use of antibiotics is most effective if given early in the course of the infection itself. Once this reaction has occurred in the kidney a week or 10 days after the original infection, it is questionable whether antibiotics can any longer effect the course.

ANNOUNCEMENTS

Certificate Ceremony and Award of Thesis Prize

On June 14 certificates were awarded to 23 Fellows who had completed their formal training in the following fields: Surgery: K. L. Allen, R. E. Allen, G. M. Brown, Jr., A. E. Greer, A. H. Robnett. Orthopedics: H. W. O'Dell, J. F. Rudolph, Jr. Urology: R. S. Graves, J. A. McClure. Ophthalmology: M. L. Helfrich, Jr., W. J. McGannon. Otolaryngology: F. C. Meadows. Anesthesiology: T. C. Hardy. Pathology: G. F. Stevenson. Internal Medicine: George Arack, R. V. Edwards, J. R. Evans, F. A. Goss, J. H. Perry, III, S. D. Splitter, A. N. Wiseley. Neuropsychiatry: J. A. Hunter. Radiology: E. H. Bryson.

At the same ceremony the 1950 Lower Fellowship Thesis Prize was presented to Dr. Charles J. Devine, Jr., for his paper entitled *A Study of Alkali Reserve in Children*. This prize was established in 1935 by Dr. William E. Lower.

APPOINTMENTS

Dr. Victor G. de Wolfe has been appointed to the staff in the Department of General Medicine. Dr. de Wolfe attended Princeton University, receiving his A.B. degree from that institution in June 1940. He graduated in medicine from the College of Physicians and Surgeons, Columbia University, in 1943. Dr. de Wolfe interned at the Roosevelt Hospital, New York, and served residencies in the New York Hospital and the Bronx Veterans Administration Hospital. He was in military service from 1944 to 1946. He belongs to several medical societies and has contributed articles to the medical literature.

Dr. R. B. Turnbull, Jr., has been appointed to the staff in the Department of General Surgery. Dr. Turnbull obtained his Bachelor of Arts degree from Pomona College in 1936 and the Degree of M.D.C.M. from McGill University Faculty of Medicine in 1940. He served residencies in Gorgas Hospital, Panama, and was a fellow at the Cleveland Clinic for a year preceding his appointment to assistant staff in 1949. From 1943 to 1946 Dr. Turnbull was with the First Marine Division. His principal professional interest is in the field of colon and rectal surgery.

On July 1 Dr. David C. Humphrey was appointed to the staff in the Department of General Medicine. He attended the University of Kansas, graduating from college in 1939 and from medical school in 1943. Dr. Humphrey served an internship at the Cincinnati General Hospital, a residency in pathology at the University of Cincinnati, and a fellowship at the Cleveland Clinic from 1947 to 1949 when he became a member of the assistant staff. He was in the Navy during 1945 and 1946. Dr. Humphrey has written several articles for the medical literature.

THE FRANK E. BUNTS EDUCATIONAL INSTITUTE

A continuation course will be presented on
Thursday, Friday, and Saturday, September 21, 22, and 23, 1950

PRACTICAL PROBLEMS IN GENERAL MEDICINE

Tentative Program

Thursday, September 21, 1950

8:00-8:30 a.m. . Registration.
8:30 a.m. . . . Clinical Conference.
9:30 a.m. . . . Treatment of Functional Indigestion . . . . . E. N. COLLINS, M.D.
9:50 a.m. . . . Needle Biopsy in Diagnosis of Liver Disease . . H. R. ROSSMILLER, M.D.
10:10 a.m. . . . Evaluation of Liver Function Tests . . . . CHARLES H. BROWN, M.D.
10:30 a.m. . . . Pancreatitis . . . . . JOHN F. WHITMAN, M.D.
10:50 a.m. . . . Treatment of Ulcerative Colitis and Regional Enteritis . . . . . E. N. COLLINS, M.D.
11:10 a.m. . . . Management of Acute Intestinal Obstruction . . . S. O. HOERR, M.D.
11:30 a.m. . . . Newer Drugs in Treatment of the Pneumonias . . . . . H. S. VANORDSTRAND, M.D.
11:50 a.m. . . . Bronchogenic Carcinoma . . . . . DONALD B. EFFLER, M.D.
12:10 p.m. . . . Questions and Discussion.
12:30 p.m. . . . Luncheon—Courtesy of the Cleveland Clinic.
1:30 p.m. . . . Treatment of Status Asthmaticus . . . . . C. R. K. JOHNSTON, M.D.
1:50 p.m. . . . The Headache Problem . . . . . LEONARD L. LOVSHIN, M.D.
2:10 p.m. . . . Pathogenic Basis of the Treatment of Hypertension . . . . . E. BRAUN-MENENDEZ, M.D.
Director of the Institute for Biology and Experimental Medicine, Buenos Aires, Argentina.
2:40 p.m. . . . Treatment of Hypertension . . . . . IRVINE H. PAGE, M.D.
3:00 p.m. . . . Diagnosis and Treatment of Pyelonephritis . . . R. D. TAYLOR, M.D.
3:20 p.m. . . . Renal Function Tests . . . . . A. C. CORCORAN, M.D.
3:40 p.m. . . . Clinical Experience with the Artificial Kidney WILLEM J. KOLFF, M.D.
4:00 p.m. . . . Panel Discussion: Treatment of Peptic Ulcer . . . . . .
Drs. H. R. Rossmiller, C. H. Brown, George Crile, Jr., and S. O. Hoerr with Dr. E. N. Collins as moderator.

GUEST SPEAKER

8:00 p.m. . . . The Rickettsial Diseases . . . . . M. A. BLANKENHORN, M.D.
Professor of Medicine, University of Cincinnati, Cincinnati, Ohio

Friday, September 22, 1950

8:00 a.m. . . . Clinicopathological Conference.

9:00 a.m. . . . Differential Diagnosis of Retroperitoneal Masses . . . . . WILLIAM J. ENGEL, M.D.

9:20 a.m. . . . Clinical Significance of Hematuria . . . . CHARLES C. HIGGINS, M.D.

9:40 a.m. . . . Management of the Obese Patient . . ROBERT W. SCHNEIDER, M.D.

10:00 a.m. . . . The Sterile Couple . . . . . E. PERRY MCCULLAGH, M.D.

10:40 a.m. . . . The Macrocytic Anemias . . . . . DONALD W. BORTZ, M.D.

11:00 a.m. . . . Differential Diagnosis and Treatment of Purpuric States . . . . . JOHN D. BATTLE, M.D.

11:20 a.m. . . . The Leukemias . . . . . DONALD W. BORTZ, M.D.

11:40 a.m. . . . Radioactive Iodine in the Treatment of Hyperthyroidism . . . . . CHARLES E. RICHARDS, M.D.

12:00 noon . . . Thyroiditis and Cancer of the Thyroid . . . GEORGE CRILE, JR., M.D.

12:20 p.m. . . . Questions and Discussion.

12:30 p.m. . . . Luncheon—Courtesy of the Cleveland Clinic.

1:30 p.m. . . . Treatment of Early Syphilis . . . . . E. W. NETHERTON, M.D.

1:50 p.m. . . . Treatment of Late Syphilis . . . . . GEORGE H. CURTIS, M.D.

2:10 p.m. . . . Treatment of Depressed States . . . . . LOUIS J. KARNOSH, M.D.

2:30 p.m. . . . Treatment of Meningitis . . . . . .

2:50 p.m. . . . Diagnosis of Brain Tumor . . . . . W. JAMES GARDNER, M.D.

3:10 p.m. . . . Rehabilitation of the Hemiplegic Patient . . SHELBY G. GAMBLE, M.D.

3:30 p.m. . . . Panel Discussion: Diabetes Mellitus
Drs. R. W. Schneider and C. E. Richards with Dr. E. P. McCullagh as moderator.

4:30 p.m. . . . (Subject to be chosen) . . . . . D. W. PICKERING, M.D.
Director of the Medical Unit, St. Mary's Hospital, London, England

5:30 p.m. . . . Cocktail Hour, Wade Park Manor

Saturday, September 23, 1950

8:30 a.m. . . . Problems in Roentgenologic Diagnosis . . . C. ROBERT HUGHES, M.D.

9:00 a.m. . . . Diagnosis and Treatment of Disseminated Lupus Erythematosus . . . . . JOHN R. HASERICK, M.D.

9:20 a.m. . . . The Use of Anticoagulants . . . . . VICTOR G. DE WOLFE, M.D.

9:40 a.m. . . . Thrombo-angiitis Obliterans and Arteriosclerosis Obliterans . . . . . FAY LEFEVRE, M.D.

10:00 a.m. . . . The Electrocardiogram in Electrolyte Imbalance . . . . . WILLIAM L. PROUDFIT, M.D.

10:20 a.m. . . . Prophylaxis of Subacute Bacterial Endocarditis . . . . . A. CARLTON ERNSTENE, M.D.

10:40 a.m. . . . Prophylaxis of Rheumatic Fever . . . . . C. H. RAMMELKAMP, M.D.
Associate Professor of Preventive Medicine, Western Reserve University

11:00 a.m. . . . Panel Discussion: Treatment of Heart Disease . . . . . .
Drs. D. W. Pickering, W. L. Proudfit, and Fay LeFevre with Dr. A. C. Ernstene as moderator.

REGISTRATION BLANK

THE FRANK E. BUNTS EDUCATIONAL INSTITUTE ....., 1950
Cleveland Clinic Building
2020 East Ninety-third Street
Cleveland 6, Ohio

Please register me for the course on "Practical Problems in General Medicine" which is to be given September 21, 22, and 23, 1950. (Registration Fee is $15.00)

I am enclosing check for $5.00 and the remainder will be paid on Registration, September 21.

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SKIN GRAFTS IN MASTOID CAVITIES

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ALTHOUGH skin grafting of mastoid cavities is not a new procedure, it is only in recent years that improvement in technic and the advent of antibiotics have made it practical and widely accepted. Previously, failures were numerous and the end result disappointing. This paper is presented (1) to demonstrate a relatively simple technic which gives uniformly good results, (2) to illustrate the reduction in postoperative care, and (3) to determine the ultimate effect of skin grafts placed inside the mastoid cavity.

Skin grafting in mastoid defects was first advocated in this country by Mosher[1] in 1911 (although it had been used as early as 1889 in Germany, where the procedure was both praised and condemned). Mosher's original technic advocated dissection of a crescent-shaped piece of skin from the posterior surface of the auricle, leaving it attached at the upper border of the postauricular sulcus. This pedicle flap, about ⅛ inch wide, was laid into the defect and the postauricular incision closed with drains inserted through the wound. In 1917 he revised this technic, using a free skin transplant applied to a paraffin basket mold made at the time of surgery. The mold and paraffin basket were removed on the fourth postoperative day through the external meatus.

In 1918, Kahn[2] recommended Thiersch grafts which he applied through the meatus after closure of the postauricular wound. He created an ingenius instrument for this purpose. Later,[3] he advocated a pedicle flap which he dissected from the posterior border of the postauricular incision.

Many variations of Mosher's original paraffin basket mold have been used. De River[4] and Israel[5] advocated the use of dental compound molded to fit the cavity. The graft was placed on the mold and fixed in the cavity. The incision was left open until the fourth postoperative day, at which time the mold was removed and the incision closed under local anesthesia. Daggett and Bateman[6] and Cunning[7] advocated secondary grafting on the fourteenth day, after granulation tissue had formed, believing that the graft was more likely to "take". Ziegleman[8] utilized the periosteum from the mastoid area, superimposed a graft thereon, and placed these within the defect. Shambaugh[9] advocated the paraffin mold in modified as well as radical mastoidectomy.

With the advent of endaural mastoid surgery, the problem of grafting was simplified because of better exposure of the mastoid cavity, and because this approach permits easy removal of the packing postoperatively. In addition, the use of the dental bur is considered to facilitate greatly the number of "takes"

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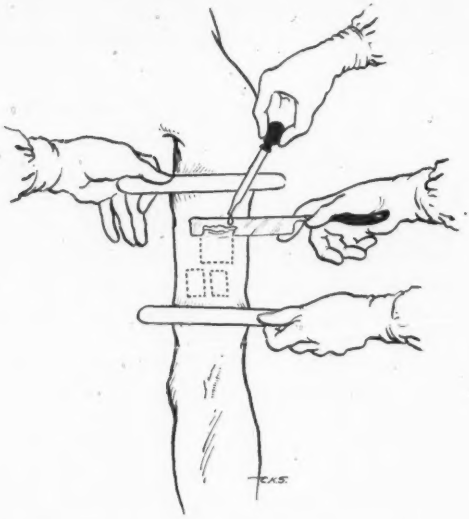

Fig. 1. Technic employed in removal of skin; saline projected onto razor blade to float grafts.

in grafting; this is probably due to the fact that the bur, revolving at a fast rate, gradually erodes the bone, leaving the extremely small vessels patent. On the other hand, the relatively slow moving, blunt chisel compresses the bone, thereby occluding the vessels.

Since 1946 we have employed skin grafts in more than 150 cases, including both radical mastoid and fenestration operations. In none of these has a graft failed to survive and the tendency to extensive granulation has been greatly reduced. Postoperative care has been shortened to an average of 4 to 6 weeks, as contrasted with 2 to 4 months prior to the use of this method. The shortened convalescence, and the decrease in the number of dressings needed during hospitalization, have saved many hours' work.

The following technic is now employed routinely. Ear cultures are made and, in the case of chronic otitis media, appropriate antibiotic therapy is begun prior to surgery. Patients about to undergo a radical mastoidectomy receive penicillin and dihydrostreptomycin or aureomycin. Fenestration cases are treated with penicillin, which is begun 24 hours prior to surgery. Antibiotic therapy is continued throughout the period of hospitalization.

At surgery, a split-thickness graft is taken from the anterior surface of the arm. Split-thickness is used for two reasons: (1) the most active reproduction of cells in the skin, as evidenced by the many mitotic figures, occurs in the lowest part of the prickle cell layer, and (2) the nourishment of the meager blood supply beneath the graft would not reach this layer in sufficient amount if full-thickness grafts were used.[10] The arm most frequently chosen is the

one corresponding to the ear to be operated upon because the opposite arm is used by the anesthesiologist for the blood pressure cuff and intravenous medication. The skin of the arm is cleansed with ether and alcohol. Strict aseptic technic is followed throughout.

An assistant holds the skin taut above and below the donor area with sterile tongue depressors, thereby affording a flat surface from which the skin is obtained with a sharp straight razor. A stream of saline is projected from above onto the razor blade to float the graft (fig. 1). The razor is used in preference to a dermatome because no glue-like substances are necessary which might interfere with growth of the graft, because thinner skin can be obtained, because the method is more rapid, and grafts of accurate and uniform thickness can be secured. The removed skin is placed in normal saline at room temperature and saved for grafting. The donor site is covered with fine mesh gauze impregnated with scarlet red ointment and a pressure dressing is applied. This dressing is left undisturbed for 6 days, then is replaced by vaseline gauze for 2 to 3 days; no further dressing is needed. No scar is formed if these rules are adhered to. Caution should be exercised in the depth of the graft. Deep grafts will cause scarring and keloid formation on the arm.

After the skin is removed, a radical endaural mastoidectomy is performed and, in the case of fenestrations, the fenestrum is created and the skin flap from the external canal thinned with iridectomy scissors. The mastoid cavity should be prepared without ridges and depressions if possible, and the bone roughened with the dental bur. (This will have been accomplished if burs are used for the endaural surgery.)

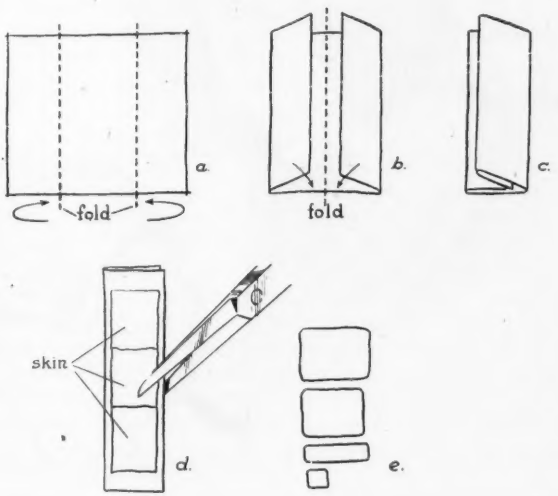

FIG. 2. Method of preparing parresinized gauze and skin grafts for application.

The Application and Placement of the Grafts

The previously obtained skin is placed, raw surface outward, on parresinized gauze mesh which has been folded so that no cut edges are visible. Both skin and gauze are cut into strips which will fit the cavity. They are flooded with saline with a medicine dropper to prevent curling and contraction of the skin (fig. 2). These pieces of skin, with the gauze approximated, are placed in the cavity so that their edges are as close together as possible without overlapping (fig. 3a). A small flat instrument such as a periosteal elevator is used to work the grafts into apposition where they are secured by placing small pieces of vaseline-impregnated gauze (rolled in sulfathiazole crystals) tightly against the graft-bearing mesh. The entire cavity is grafted in this manner, 5 to 6 pieces of skin approximately 1 by 2 cm. being used. It is then firmly packed with the grafts in proper position, the vaseline gauze pledgets of varying sizes fitting the contour of the cavity (fig. 3b). This prevents over-pressure on some areas. A pressure dressing is applied externally.

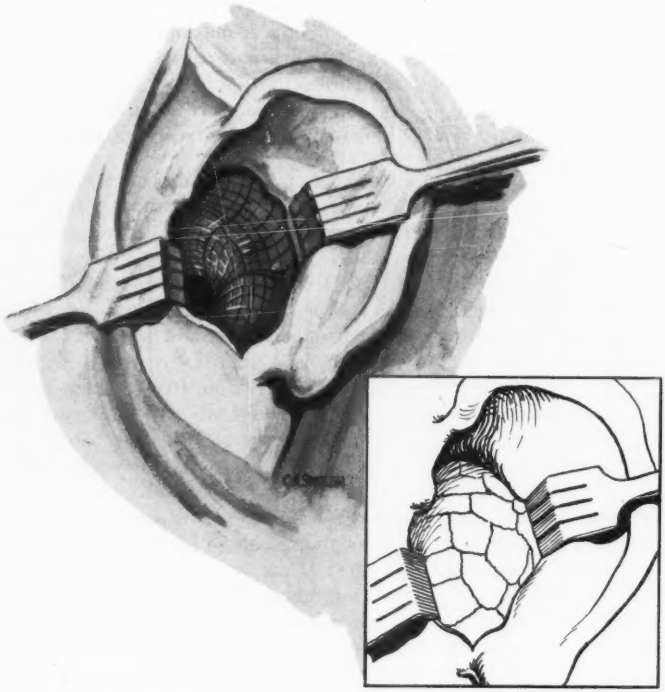

Fig. 3. (a) Schema of endaural mastoid cavity showing grafts in place. (b) Cavity packed with vaseline gauze pledgets.

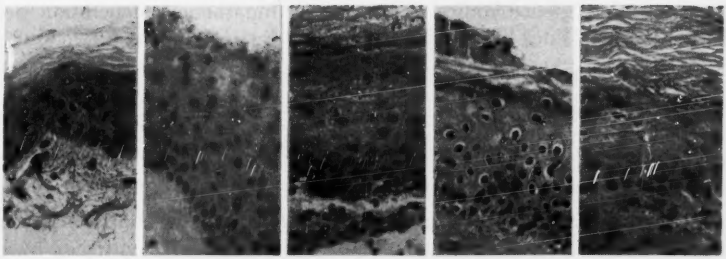

Fig. 4. Photomicrographs of epidermis at surgery and at 2, 4, 6 and 8 weeks.

The packing inside the cavity is not disturbed until the sixth postoperative day, although the outer dressing is changed every second day to prevent pressure necrosis of the external ear. Care should be taken to pad the external ear sufficiently.

When the packing is removed from the mastoid cavity, the grafts have become adherent and the cavity is almost completely epithelialized. The packing must be removed with care else the not-too-firmly-attached, more external grafts may be loosened. The center pledgets are always removed first and the peripheral supporting pledgets and parresinized gauze last. Subsequent postoperative care consists of cleaning out small amounts of serous drainage every 2 days for 1 week. The cavities are completely healed in 3 to 4 weeks and no further treatment is needed. It is rarely necessary to pack the cavity postoperatively. In no case has there been uncontrollable granulation, or failure to obtain a dry ear. It is exceedingly important that the patient obtain a dry ear whether a radical mastoidectomy or a fenestration has been performed.

Since the inception of skin grafting there has been discussion as to the ultimate effect of split-thickness skin transplants in mastoid cavities. Most observers believe that the skin actually remains viable and grows, while a minority feels that the graft acts merely as a depressor of granulation tissue and that the epithelialization occurs from the flap and sides by extension.

In an effort to clarify this point, biopsies were taken from the center of known graft areas at 2, 4, 6, and 8 weeks and the tissue analyzed by the Department of Pathology. In every case the report was "viable skin" (fig. 4), as evidenced by the normal staining reaction, mitoses in the prickle cell layer, and the presence of all layers of epidermis. Therefore, we must conclude that there is ample evidence to prove that the grafts do remain viable and do grow.

It is interesting to note that sensation returned to the skin at the end of 4 weeks. The first biopsy at 2 weeks was absolutely painless, at 4 weeks slightly painful, at 6 weeks moderately painful, and at 8 weeks the pain was fairly severe. This is in accordance with the findings of McCarroll[11] on the return of sensation in transplanted skin.

Another interesting observation was that at 2 weeks the biopsy was relatively bloodless, but with each succeeding biopsy more blood was encoun-

tered.[12] Such evidence indicates that the sympathetic regeneration occurs along the vessels, since bleeding in each case was controlled by adrenalin pack.

Summary

1. A practical method of grafting mastoid cavities is outlined.

2. Convalescent time and postoperative care have been greatly reduced.

3. Evidence is presented which substantiates the belief that split-thickness grafts survive and grow when transplanted into mastoid cavities.

4. A dry ear can be obtained with a greater degree of certainty than by any previous method we have attempted.

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THE USE OF BRITISH ANTI-LEWISITE (BAL) IN THE TREATMENT OF DIABETIC NEUROPATHY

Clinical Study — Preliminary Report

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BRITISH anti-lewisite (BAL) has been administered to 22 diabetic patients in the course of the last year, in an attempt to appraise its clinical value in the treatment of various neurologic complications of diabetes. This study was prompted in part by the report made by Furmanski[1] several years ago which indicated that some peripheral neuropathies other than those associated with heavy metal intoxication might be helped by the administration of BAL. At that time he reported 3 cases of peripheral neuropathy improved by its administration. It was postulated that neuropathies might represent biochemical disorders within the neuron, consisting of impairment of enzymatic function. Since the etiology and treatment of diabetic neuropathy require both clarification and improvement, it was decided to test the virtues of BAL in such cases.

This report summarizes the results obtained in these 22 patients, discusses briefly the theoretical aspects of the action of sulfhydryl compounds, interjects a word of caution regarding its use, and emphasizes its limitations.

Before the study was undertaken a number of important considerations required critical analysis. The first of these concerns the pharmacologic properties of BAL, only the more pertinent of which will be discussed. BAL (2, 3-dimercaptopropanol) is recognized as an extremely potent compound containing two sulfhydryl radicals; these sulfhydryl radicals have a great affinity for heavy metals. Many essential enzyme systems contain heavy metals within their chemical structures. Webb and Von Heyningen[2] studied the effects of BAL on enzyme systems, and showed that 7 were strongly inhibited by BAL. For example, polyphenol oxidase becomes inactivated in the presence of BAL but is reactivated when copper is added. Carbonic anhydrase, when inactivated with BAL, regains its activity upon the addition of zinc. BAL decreases the respiration of tissue slices and inhibits the activity of cytochrome C; in sufficient concentration it also destroys the activity of insulin,[3] apparently by interfering with its disulfide linkage.

Heavy metals usually produce toxicity because of their great affinity for sulfhydryl radicals present in the prosthetic group of many essential enzymes. For example: the concept has been accepted generally that trivalent arsenic blocks the metabolic function within the spirochete, as well as in human tissues, by combining with such sulfhydryl groups within enzymes. The application of BAL to the treatment of arsenical intoxication was based on its ability to

supply competing sulfhydryl radicals in order to protect, as well as to reactivate, previously affected enzyme systems. The reversibility of such biochemical processes is confirmed amply by studies such as those to which we have referred.

It is evident from animal experimentation[4] that the administration of heavy metals prior to the administration of BAL increases the tolerance of the animal for BAL. Toxic side effects, common in small doses in normal animals, do not result when much larger doses are given animals intoxicated by heavy metal. It is thus apparent that heavy metals are antidotes for BAL, and that BAL and other sulfhydryl compounds are antidotes for heavy metals. It appears evident, too, that the doses of BAL recommended for the treatment of heavy metal intoxication cannot necessarily apply to persons with diabetes, since it has not been ascertained that the neurologic manifestations of diabetes bear any relationship to heavy metal poisoning. The important initial consideration in this observation was the safety of BAL administration, particularly in the treatment of the diabetic patient. Throughout the entire investigation the doses employed were always maintained at a level far below the quantities recommended for the treatment of heavy metal poisoning. Exceptional care and precautions were observed throughout in the event that toxic manifestations (in terms of alterations in pulse, blood pressure, respiratory rate, and alterations in body chemistry) might become manifest.

Results

Twenty-two patients with diabetic neuritis have been treated with BAL during the course of the last year; each has been hospitalized during the period of therapy. Every patient had received varying periods of diabetic control with improvement in nutrition, and many had taken additional vitamins prior to BAL therapy. All had failed to respond to these customary measures of treatment. BAL was administered intramuscularly in an initial dose of 50 mg. on the first day and was increased to 100 mg. on the second day. The dosage generally remained at 100 mg. once or twice per day, although occasionally 3 doses were prescribed within a 24 hour period. The average duration of treatment was from 7 to 14 days. The results have been interesting and promising and, although not consistently favorable, have been sufficiently encouraging to justify a report. Among the 22 patients treated, 12 were definitely improved (table 1), and 10 were unimproved (table 2).

Among the 12 patients improved there were 9 (cases 1 through 8 and case 12) who had an accentuation of pain beginning from 5 to 15 minutes after the injection on almost every occasion. The intensification of the pain followed the distribution of the involved nerve or nerves, and persisted for from ½ to 2½ hours, following which the discomfort diminished or completely disappeared. Usually the pain became intensified following each subsequent injection and, as treatment continued, the pain disappeared completely except for the time immediately following injection. Occasionally it was noted that, after 4 or 5 injections (particularly if the size of the dose were kept constant), return

of the pain was not experienced until the size of the dose was increased, at which time the original type of pain might return. Patients did not always experience this phenomenon following each injection; it did not always appear after the initial dose, and sometimes not until after the second or third dose. This phenomenon was observed in 9 patients, none of whom were informed that such an occurrence might be anticipated. One of these was a physician (case 7) whose verbatim description of his subjective experience is included herewith:

"Fifteen minutes following each injection (timed by the clock) there was an abrupt modification in the subjective distress over the area afflicted. Anesthesia, or at times intense pain, occurred over the involved nerve segments as the reaction wore off; during the next 30 to 60 minutes the feet became warm and comfortable. Hyperesthesia and pain gradually diminished. At the termination of 11 injections some anesthesia is still present in the left great toe, but to a noticeably diminished extent. There is no hyperesthesia, no paresthesia, no burning, no deep-seated pain and no anesthesia of the remaining portion of the feet. There is no nocturnal exacerbation of symptoms. Minimal edema of the lower legs and ankles has disappeared. The skin of the feet and legs which showed trophic changes has assumed a healthy appearance."

Each of these patients experienced subjective improvement and some complete disappearance of pain after 10 to 14 days of treatment. Eight of the 9 have remained free of discomfort for periods of 1 month to as long as a year. The results have been uniformly satisfactory in this particular group with but one exception, a patient (case 12) who experienced an accentuation of the pain on 2 occasions, although treatment was conducted for a 13 day period. His symptoms disappeared but promptly recurred 2 days after treatment ceased, and he failed to respond to a second course of therapy. He has since committed suicide.

Among the 12 patients who improved, there remain 3 (case 9, 10 and 11) who obtained definite alleviation of pain, numbness, or burning in the lower extremities. None of these experienced accentuation of distress following any injection. In 1 patient (case 9) numbness recurred after 4 months and did not respond to a second course of treatment. In another (case 11) improvement has been maintained after a period of 4 months. The remaining patient (case 10) had complete relief from pain for a period of 6 weeks after which time it returned with original intensity; a second course of therapy was followed by complete relief for a period of 2 months, although she is at present under treatment for a third recurrence.

Among the 10 patients who were unimproved, there were 4 (cases 13, 14, 15 and 16) whose symptoms of numbness and paresthesiae had been present for 3, 4, 8 and 18 years respectively. Improvement was apparent in none, even though BAL was administered for periods of time similar to that of the first group. Therapy was interrupted in 1 person (case 21) after 5 injections had failed to cause significant alteration in the intensity of pain; this may have constituted an inadequate trial.

TABLE 1

SUMMARY OF 12 CASES SHOWING RESULTS OBTAINED IN THOSE RECEIVING GREATEST IMPROVEMENT FROM BAL THERAPY

Case	Age	Known Duration of Diabetes	Duration of Neuropathy	Duration of BAL Therapy	Total Amount of BAL Given	Immediate Result
1.	60	12 yrs.	7 mos.	13 days	1075 mg.	Accentuation of pain
2.	63	12 yrs.	6 mos.	9 days	1800 mg.	Accentuation of pain
3.	36	3 mos.	6 mos.	15 days	1700 mg.	Accentuation of pain.
4.	67	Found at time of first visit	18 mos.	10 days	900 mg.	Accentuation of pain
5.	64	14 yrs.	3 mos.	12 days	1150 mg.	Accentuation of pain
6.	56	7 yrs.	8 mos.	10 days	1300 mg.	Accentuation of pain
7.	43	9½ yrs.	2+ yrs.	11 days	375 mg.	Marked increase in pain. (See description.)
8.	54	7 mos.	1 week after diabetes was "controlled" 6+ mos.	8 days	850 mg.	Marked increase in pain each injection
9.	47	4 yrs.	3 mos.	8 days	975 mg.	Accentuation of pain
10.	58	3 yrs.	6 mos.	1st 13 days course	475 mg.	No accentuation of pain
				2nd 11 days course	1375 mg.	No accentuation of pain
11.	69	19 yrs.	5 mos.	20 days	1900 mg.	No accentuation of distress
12.	67	10 mos.	4 mos.	13 days	800 mg.	Intensification of pain after 2 injections

One patient (case 20) presented clinical evidence of severe peripheral vascular insufficiency accompanied by cyanosis of the feet upon assuming a dependent position. Advanced degrees of arteriosclerosis were demonstrated roentgenologically.

TABLE 1 (continued)

Results at End of Therapy		
Sensory	Motor	Ultimate Result
Complete absence of pain and numbness. Stopped codeine 5th day.	No change. Absent patellar and achilles reflexes.	No return of pain after 6 months.
Complete relief of pain and numbness.	Gait improved reflexes unchanged, vibratory sense unchanged.	No return of pain after 10 months.
Marked improvement. Occasional brief periods of pain.	No alterations.	No recurrence after 6 months.
Complete relief of pain, burning and numbness.	No alterations.	No recurrence after 4 months.
Complete relief of pain and burning.	No alterations.	No recurrence after 5 months.
Complete relief of pain and burning.	Diplopia improved.	Slight numbness returned after 10 mos. No pain after 1 year.
Complete relief of pain, burning and paresthesiae.	Trophic changes in skin and toe nails disappeared.	No return after 9 mos. in spite of acute peritonsillar abscess 5 mos. after therapy.
Complete relief of pain, burning and numbness.	No changes.	Therapy just completed. No return after 1 month.
Complete relief of pain and burning.	No changes.	Returned after 4 mos. Did not respond to second course.
Complete relief of pain.	No changes.	Returned after 6 weeks.
Complete relief.	No changes.	Returned after 2 months.
Complete relief of pain, coldness, dysesthesiae and feeling of constriction.	Loss of sensitivity of flesh, no motor changes.	No return after 4 months.
Complete relief of pain.	No changes.	Recurred after 2 days. No response to second course.

Another patient in the group of failures was a man whose first neurologic symptoms appeared upon awakening in another hospital after a 3 day period of unconsciousness due to insulin shock. He was thought to have suffered extensive cortical damage incident to his hypoglycemia, since he had noted

retrograde amnesia and a poor memory dating from that time. There was loss of two-point discrimination sense and astereognosis as well. Vurpas' sign, indicative of frontal lobe degeneration, was strongly positive.

Improvement failed to occur in still another patient (case 18), a man of 67 years, in whom neuritis had been present for a period of 6 months. He was totally uncooperative and objected to all forms of therapy from the beginning. There was evidence of advanced arteriosclerosis obliterans of the lower extremities, loss of vibratory sense and position sense below the knees, and absent patellar and Achilles tendon reflexes. Spinal fluid protein measured 85 mg. per cent. Repeated caudal blocks with 1 per cent procaine failed to effect relief of his pain; vascular exercises and vasopneumatic therapy were without benefit. A trial on BAL suggested initial improvement, but the patient complained so bitterly of pain at the site of injection that treatment was discontinued. A transorbital leukotomy failed to produce relief. He left the hospital under protest.

An additional patient (case 19) who failed to respond to BAL had an intercostal neuralgia with a zone of anesthesia comparing to the 9th dermatome. X-rays of the dorsal spine showed an extensive osteoarthritis. His pain was diagnosed as a parietal neuralgia, either secondary to osteoarthritis or possibly the result of diabetic neuritis. A 12 day course of BAL failed to relieve the pain, but it was immediately alleviated by the introduction of novocain into the contralateral cervical sympathetic chain. It is not clear whether diabetic neuritis or radiculitis caused by osteoarthritis occasioned the pain. This case is included, nevertheless, as a failure.

The remaining patient in this group (case 22) may not have had diabetic neuritis because fever, a rapid sedimentation rate, and a questionable destructive lesion in the 3rd lumbar vertebra were observed. Her pain was relieved by x-ray therapy.

Toxic Reactions

No serious toxic reactions occurred in a single instance. Local discomfort at the site of the injection varied from no pain at all to a severe, burning variety. The local distress was usually of short duration and not of sufficient intensity (except in the foregoing case) to discourage further injections. Inflammatory reactions at the site of injection were not evident. Intensification of the pain, which appeared at first to indicate an undesirable side effect, may actually represent a good prognostic sign, since the persons experiencing this reaction obtained the greatest amount of improvement and have shown the least tendency toward recurrence. Alterations in respiratory rate, blood pressure, or pulse and body chemistry did not occur under BAL therapy. There was no alteration in insulin requirements in a single patient. This conceivably might not be true should larger doses of BAL be employed, but this investigation was not for the purpose of ascertaining the maximum level of tolerance of diabetic persons to intramuscular BAL therapy.

Discussion

The frequent occurrence of neurologic abnormalities in diabetic patients prompted earlier students to consider the central nervous system as the site of the basic lesion in diabetes. In 1864 De Calvi first postulated that the neurologic manifestations were complications of the diabetic state. Since that time much has been written concerning the nervous system in diabetes. Lesions have been described in the brain, the spinal cord, posterior nerve roots, sympathetic ganglia, and peripheral nerves. It would appear that no part of the nervous system is entirely immune, although symptoms are noted more often in the lower extremities.

Little is known concerning the etiology and pathology of diabetic neuropathy. The neurologic features evident in diabetic patients represent a far from clear-cut syndrome. Because this syndrome may be diffuse or disseminated, often representing a bizarre picture, it is difficult to evolve an accurate clinical classification of diabetic neuropathy. It may occur with many symptoms and few signs, with few symptoms and many signs, or a combination of both. It is for this reason, in part at least, that any new approach at therapy makes accurate evaluation impossible.

Widespread involvement of the nervous system may be manifested by such distressing symptoms as neuropathic foot simulating Charcot's joint, nocturnal diarrhea, bladder paralysis, abnormal pupillary reaction, and ocular muscle palsy. Complications that have advanced to this degree are probably irreversible.

A number of explanations for the neurologic manifestations of diabetes have been offered, including vitamin deficiency, dehydration, toxic factors, hyperglycemia, cachexia, ketosis, and arteriosclerosis, either within the nutrient vessels of the brain or spinal cord or within the vasa neurorome. More than one factor is undoubtedly important and the pathogenesis of diabetic neuritis cannot be fully appreciated until examination of considerable histologic material has been made from patients intensively studied during life. While considerable attention has been devoted to the use of vitamin B and other food supplements in treatment of this complication, results have not been encouraging.

Careful histologic studies of the nervous system in diabetes made by Woltman and Wilder[5] disclose the presence of arteriosclerosis of the nutrient vessels of the nerves which they consider an important factor in the production of diabetic neuritis. While undoubtedly important, arteriosclerosis may be the principal limiting feature in the development of any therapeutic procedure capable of producing uniformly good results until vascular degeneration can be prevented or overcome. Thus the cause of the complication is as obscure as the pathogenesis of the underlying disease.

A further limiting factor which prevents any accurate conclusion in the establishment of a new therapeutic tool for the treatment of diabetic neuritis is the variability in the behavior of the complication. It is unrelated to the severity of the diabetes or to the insulin requirement. Neuritic symptoms may

TABLE 2
SUMMARY OF 10 CASES TREATED WITH BAL SHOWING LITTLE OR NO IMPROVEMENT

Case	Age	Known Duration of Diabetes	Duration of Neuropathy	Duration of BAL Therapy	Total Amount of BAL Given	Immediate Result
13.	50	6 yrs.	4 yrs.	11 days	2100 mg.	? Improvement
14.	58	11 yrs.	3 yrs.	8 days	860 mg.	? Improvement
15.	65	3 yrs.	18 yrs.	10 days	2400 mg.	None
16.	61	9 yrs.	8 yrs.	10 days	2100 mg.	None
17.	57	13 yrs.	8 mos.	10 days	550 mg.	None
18.	67	4 yrs.	6 mos.	5 days	300 mg.	None. Refused further doses
19.	62	10 yrs.	3 mos.	9 days	1200 mg.	None
20.	69	3 yrs.	2 yrs.	9 days	1600 mg.	None
21.	53	21 yrs.	4 mos.	4 days	350 mg.	None
22.	54	4 yrs.	1 mo.	24 days	4800 mg.	None

be the first indication of the presence of diabetes, may never occur during a lifetime of diabetes, or may appear only as a late manifestation. Once present, diabetic neuritis may improve slowly with the management of the underlying hyperglycemia and glycosuria. Conversely, it may make its first appearance after the disease has been brought under control; however, in the majority of instances, it runs a chronic course which appears to be its most constant feature. Seldom do the symptoms change appreciably over the period of a few weeks but rather slowly over a period of months or years. This particular feature of diabetic neuritis is emphasized when reviewing the results of cases treated with BAL.

Since diabetic neuritis occurs among well-controlled diabetic patients as well as among those who are poorly controlled, diet and insulin, still the basic essentials in the management of any complication of diabetes, are often inadequate methods of treatment. Vitamin therapy has not produced recovery

TABLE 2 (continued)

Results at End of Therapy	Ultimate Results	Remarks
None	None	Neuritic symptoms present 4 years.
Pain gone	Symptoms returned in 2 weeks	Neuritic symptoms present 3 years.
None	None	Neuritic symptoms present 18 years.
None	None	Neuritic symptoms present 8 years.
None	None	Onset of symptoms dated to insulin shock. Retrograde amnesia, loss of 2 point discrimination astereognosis + Vurpas' sign.
None	None	Uncooperative. Failed to secure relief from caudal blocks, vasopneumatic therapy and transorbital leukotomy.
None	None	Extensive osteoarthritis dorsal spine. Pain relieved by novocain injection of contralateral cervical sympathetic chain.
None	None	Extensive arteriosclerosis of leg vessels. Dependent cyanosis. Oscillometric readings ¼ right, ½ left.
None	None	Discontinued because pain was atypical and no altered by injections (inadequate trial).
None	None	Diagnosis questioned. Had rapid sed. rate, fever, ? destructive lesions lumbar spine. Pain relieved by x-ray therapy.

either uniformly or consistently and, in general, has been disappointing. Because of the multiplicity of the problem of diabetic neuritis and the lack of uniformly satisfactory therapeutic procedures for its relief, the investigation of any new adjunct to therapy seemed desirable and justifiable.

The experience gained in the study of these 22 cases does not permit final conclusions. Several observations, however, appear to be of sufficient importance to justify further investigation of the real value of BAL therapy. The first of these is the intensification of the pain following the injections of BAL in those patients who received maximum benefit. Experiments wherein radioactive BAL is administered[6] demonstrate its rapid elimination, the greater part being quickly metabolized and excreted in the urine. It enters the circulation from an intramuscular site within 5 minutes and reaches a maximum blood level within an hour. A constant blood level is obtained for the first 2 hours, is reduced by one-half at the end of 3 hours and to one-third at the end

of 7 hours. Eighty per cent enters the circulation and is distributed throughout the body 1 hour after injection. It is entirely gone from its intramuscular site at the end of 6 hours. Only a minute amount is excreted by the lungs. Forty-five per cent of the total is in the urine within 6 hours, and 81 per cent within 24 hours. Hence it is not significantly cumulative in 4 hour doses. Side effects, when they appear, are transient and when symptoms do occur disappear in 2 to 3 hours.

When one compares the rate of absorption of BAL and its known blood concentrations after administration with the time of appearance and the duration of the intensification of pain in patients who obtained the greatest improvement from treatment, the correlation seems more than mere coincidence.

The other feature deserving further consideration is the degree of improvement manifest within a short period of time. Gradual disappearance of pain over a period of 7 to 14 days of BAL therapy demonstrates a striking contrast to all other therapeutic measures employed in the past. The reappearance of pain at intervals following a course of therapy, and the subsequent response to a second course, at least in some patients, are matters of additional interest.

These observations suggest that whatever benefit sulfhydryl compounds may exert in management of painful neuropathy of diabetes must come about through a biochemical change rather than by a regeneration of damaged nerve tissue. The complete failure experienced in some cases although disappointing is not necessarily surprising, particularly if multiple factors are responsible for the development of the neurologic complications. It is understandable that, where arteriosclerosis is the major factor responsible for nutritional changes within the nerve fibers, anatomic and structural changes may well have advanced to an irreversible stage.

An especially disappointing feature is the inability to demonstrate improvement in the neurologic signs. Although vibratory sense improved in some patients, and muscle tone in many (together with diminution of tenderness along the peripheral nerves and muscles), no constant improvement in reflexes or other neurologic signs could be elicited.

Subjective improvement in symptoms of numbness and paresthesia often could be noticed by the patient from day to day; with continued therapy, the numbness which originally might have extended to the knees would gradually become more and more peripheral, tending to persist in the feet and toes for the longest period of time. Occasionally it would remain in these areas for some days before abating, or persist in the toes permanently. Frequently, the patient would report that he was able to sleep comfortably throughout the night, that he could tolerate the weight of bed clothing against his limbs, and that his feet were no longer cold.

In one person trophic changes in the skin and nails of the lower extremities underwent profound alteration. The atrophic skin became normal in color and began to desquamate in normal fashion. Yellow discoloration of the toenails, which had been present for 2 years, gradually disappeared as the new nail grew in.

One patient with diplopia due to ocular muscle palsy experienced im-

provement but not complete disappearance of the double vision. Two patients in whom codeine addiction had been feared voluntarily discontinued the use of narcotics after 4 and 7 days respectively.

Summary

Conclusions as to the ultimate value of BAL in the management of diabetic neuritis are at present unjustifiable. The results obtained in the 22 cases reported, however, are encouraging. BAL in the doses employed was well tolerated by patients with diabetes; there was no evidence that the underlying diabetes was intensified or that the insulin requirement was altered. Undesirable side effects were limited to pain at the site of injection. Because serious side effects (known to accompany larger doses of BAL) were avoided, the maximum tolerance for BAL by patients with diabetes was not established. Since the drug is rapidly disseminated and eliminated within a period of 6 hours, it is theoretically possible that its administration every 6 hours might prove more beneficial than under the schedule employed.

The possible merits of other sulfhydryl compounds, such as glutathione, cysteine, and BAL-glycoside (BAL intrav) should be studied, particularly since the latter has a much lower LD-50 than does BAL. The great difference in response to BAL in these 2 groups of patients suggests that a better classification may be possible in cases of diabetic neuritis, and its real therapeutic value may be limited to those who experience intensification of symptoms. Inasmuch as several of the more protracted cases of neuropathy failed to respond, early treatment may be important for a better therapeutic score. Possibly the combination of earlier treatment and more frequent doses of BAL or some other sulfhydryl compound may aid materially in the management of this complication. BAL must be considered only as an adjunct to the treatment of the neuritis and the underlying therapy must consist of the management of the diabetes itself.

It is natural to assume that zinc, a constituent of all commercial insulins, might be the agent responsible for the production of the neuritis. This seems unlikely, however, since neuritis has occurred in patients who have never taken insulin, and existed long before its advent. Presumably the mechanism of BAL action in such cases bears no relationship to the removal of heavy metals from the nervous system itself.

Conclusion

Twenty-two patients with diabetic neuropathy have been treated with BAL; 12 have been relieved of their pain and, to a large extent, the subjective distress attending the neuritis. Eight of these experienced an intensification of pain following almost every injection and have remained free of recurrences. Four showed no intensification of distress but tended toward relapse. Ten patients experienced no benefit. A possible explanation for failure has been presented and a recommendation for early treatment has been advocated.

Note of Caution

For the present the size of each individual injection of BAL should be maintained at a low level until further experience indicates that larger doses can be employed safely. Since this highly volatile substance loses much of its potency upon exposure to air, the unused portion of the ampule should be discarded and a fresh ampule used for each injection. The accepted standards in the management of diabetes, including diet and insulin, should not be disregarded. BAL must be considered a possible adjunct to the management of this complication, and reserved only for those patients in whom established forms of therapy have proved ineffective.

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CHANGING TRENDS IN SURGERY OF THE COLON

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THE preoperative preparation of the bowel with sulfonamides and antibiotics, the prophylactic use of antibiotics after operation, and modern advances in surgical technic have contributed materially to the safety of operations on the colon. As a result of these advances it is possible today to perform with relative safety operations which prior to 1940 were deemed hazardous; to preserve the rectal sphincter when formerly it was often necessary to sacrifice it, and to perform primary end-to-end anastomoses in situations which at one time appeared to demand obstructive resections or complementary colostomies with their attendant inconvenience and morbidity. The purpose of this study is to evaluate the present status of the various types of operations in colon surgery.

Changes in Preparation of Colon

Prior to 1942 patients to be subjected to resections of the colon were prepared by the use of magnesium sulfate and a low residue diet. Occasionally sulfonamides were given after operation, but these were used therapeutically in the treatment of established complications and not prophylactically.

Since the war (1946) we have prepared the bowel by administration of sulfasuxidine given in doses of 3 Gm. four times daily for 7 days before operation and sometimes supplemented by streptomycin, 1 Gm. given twice daily for the last 2 days. More recently aureomycin has been used in doses of 500 to 750 mg. four times daily for 3 days. The latter is not only the most effective means of reducing the bacterial count in the stool,[1] but is also absorbed and is effective in controlling cellulitis and infection in the tissues around an ulcerating lesion.

Prophylactic Use of Antibiotics

Following operation in cases in which the bowel was opened we have routinely given penicillin in doses of 600,000 to 1,200,000 units daily for the first 2 or 3 days and recently have supplanted this by the use of aureomycin. Aureomycin appears to be more effective than penicillin in controlling infections which arise from the colon.

Gastrointestinal Intubation

Previous to 1942 it was not customary to intubate the gastrointestinal tract before resections of the colon. Since 1945 a Levine tube has been placed in the stomach just prior to operation and gastric suction is maintained for the first

24 hours to prevent distention which may result from swallowing air. In patients subjected to resection of the right colon, the intestine may be intubated prior to operation, and the tube left in place for 2 or 3 days or until it is apparent that the anastomosis is functioning. However, in the past year we have used this form of intubation infrequently and find that the Levine tube is sufficient protection.

Ambulation

Before 1945 patients subjected to resections of the colon were confined to bed for a week or 10 days. Since the war patients are urged to walk on the day of operation and to spend as much time out of bed as possible. Even patients with Rankin clamps attached to exteriorized segments of bowel are advised to be up and about.

Anticoagulants are used only rarely, chiefly in exceptionally obese individuals or in those who refuse to move about. Recognized embolism has not occurred in the group of cases to be reported. A factor in the diminished incidence of this complication may have been the strict avoidance of the use of leg veins for administration of fluid or blood, a practice which may contribute to the development of deep phlebitis. Long periods of immobilization on the operating table also may be a factor in the production of thrombosis.

Transfusion

The transfusion of blood was employed in almost all patients subjected to operations on the colon before 1942. Since 1945 we have recognized that there is a small but definite hazard in the administration of blood, and have employed transfusion only when the patient is anemic or when specific indications are present.

Changes in Technic of Abdominoperineal Resection

We have not modified the technic of combined abdominoperineal resection as developed by Miles[2] and T. E. Jones except that, since 1946, we have closed many of the posterior wounds tightly. A small catheter is left in place and is aspirated twice daily and 200,000 units of penicillin injected in the cavity following which it is clamped off. After 4 days it is withdrawn. Following this usually there is no further drainage from the wound.

Posterior wounds were packed open and were allowed to close by secondary intention prior to 1946. These wounds rarely healed within 3 months, and often 6 months or more elapsed before closure was complete. Occasionally the posterior wounds became infected and the postoperative reaction including fever and distention tended to be more pronounced because of the infection and the foreign body reaction to the large pack in contact with the pelvic peritoneum. Ambulation was impeded, and urinary complications appeared to be more common. When the wounds are closed primarily there is little or no infection, no contraindication to early ambulation, and the patients void earlier and

seem to empty their bladders more completely, possibly because they are ambulatory from the first.[3] We believe that primary closure reduces inflammatory reaction in the posterior wound and hence minimizes the tendency to pelvic phlebitis and pulmonary embolism.

Resections of Left Colon

Obstructive resection was utilized as the standard procedure for resection of lesions of the left colon previous to 1942. The Rankin clamp was left in place for from 5 to 6 days and a colostomy was established by its removal. About the sixth postoperative day a spur clamp was applied. The patient usually left the hospital between the twelfth and fourteenth days and was subjected to the inconvenience of a colostomy for 2 months at home. He then returned for closure of the colostomy which required usually another week of hospitalization.

Since 1947 we have employed resection and end-to-end anastomosis in the management of an increasing number of lesions of the left colon. We believe that a wider segment of bowel and mesentery can be resected by this method and that better protection can be assured against local recurrence of carcinoma in the abdominal wall. Except in palliative resections in patients with distant metastasis we do not believe that carcinoma below the reflection of the peritoneum should be dealt with in this manner but many lesions which lie at or just above the reflection of the peritoneum can be resected and continuity of the bowel re-established without jeopardizing the patients' possibility of cure.[4,5,6,7]

Final evaluation of low sigmoidal anastomosis is contingent upon a longer period of observation than is covered in this series.

Before 1942 we performed open end-to-end anastomosis of the colon with two rows of inverting continuous catgut sutures. This method was not safe because of the high incidence of obstruction and the occasional development of peritonitis due to leaks at the line of anastomosis. At this time, therefore, obstructive resection was a safer procedure.

In the past 2 years, with the development of better means of preparing the bowel we have employed the interrupted suture technic for open anastomosis. An inner row of interrupted chromic 000 catgut sutures through all layers, with knots on the inside, inverts the bowel and is reinforced by an outer row of interrupted silk sutures. There has been only one patient who gave evidence of localized or spreading peritonitis, no abscesses were encountered, and there has been only 1 case in which there was any evidence of obstruction in 90 consecutive resections performed by this technic. The bowels usually move spontaneously on the second or third day, and the usual period of hospitalization after operation is approximately 9 days.

Right Colectomy

In the past few years we have avoided gross contamination of the retroperitoneal space in resections of the right colon and have noticed a striking

decrease in morbidity. Since the resistance to infection of the peritoneal cavity is much greater than that of the retroperitoneal tissues, we have protected the vulnerable retroperitoneal area from which the cecum and ascending colon have been removed by closing the peritoneum over it and packing it off before the bowel is transected or the abdominal cavity contaminated. Postoperative obstruction has not occurred in these cases. All ileocolonic anastomoses were of the open type made by the end-to-side, side-to-side, or end-to-end technic.

Subtotal Colectomy

In polyposis of the colon or in severe ulcerative colitis we have been impressed with the relatively high morbidity which attends procedures of more than one stage, in which operations must be performed in the presence of ileostomies or colostomies. It is difficult to prevent contamination from the previously exteriorized ends of bowel, and intestinal obstruction secondary to localized peritonitis has been a common complication. For this reason, and because in acute ulcerative colitis we believed that the patients would benefit if the major portion of the diseased colon could be removed at the same time the ileostomy was established, we have begun to perform end ileostomy with skin graft and removal of the right colon, transverse colon, descending colon and as much as possible of the sigmoid at a single operation through an elliptical transverse incision just below the umbilicus. The stump of the sigmoid is brought out just below the umbilicus in the midline where it can be removed with an ellipse of skin and without contamination at the time of the later abdominoperineal resection. The retroperitoneal space is completely re-peritonealized before the bowel is transected so that the operation of colectomy is, for all practical purposes, an aseptic one. The course of these patients has been remarkably smooth and has justified continuation of the one stage partial colectomy followed by combined abdominoperineal resection as opposed to the former method of performing the operation in 4 stages (ileostomy, right colectomy, left colectomy, and combined abdominoperineal resection).

Protection of the Wound from Contamination

Dr. T. E. Jones always emphasized the importance of protecting the wound from contamination, and invariably protected the entire wound, not just the skin edges, with gauze packs. We have added a layer of rubber between the gauze, and wall off the entire wound completely before incurring any contamination from the bowel. A clean set of gloves and instruments are used for closure, to reduce further the danger of contamination to the abdominal wound.

Results

Two hundred and seventy-four consecutive resections of the colon have been performed by the authors with no deaths in the hospital following operation. (This series was broken when a patient died in August 1950, 5 days after subtotal colectomy. She had been in the terminal stages of acute toxic

ulcerative colitis with serum albumin 0.6 mg. per hundred cc., accompanied by massive edema. Death was the result of massive bilateral atelectasis, probably exacerbated by the hypoproteinemia.)

274 CONSECUTIVE RESECTIONS OF THE COLON

Operative Procedure

Combined abdominoperineal resection (Miles)	84
Abdominoperineal pull-through	6
Resection with primary anastomosis	90
Obstructive resection (Rankin)	35
Right colectomy (with primary ileocolonic anastomosis or ileostomy)	38
Left colectomy (second stage colectomy—no anastomosis)	5
Total colectomy (1 stage—rectum remaining)	16
Hospital deaths	0
	274

REASON FOR OPERATION

Cancer	225
Ulcerative colitis	32
Polyposis	9
Diverticulitis	6
Megacolon	2
	274

The average period of postoperative hospitalization for patients with uncomplicated combined abdominoperineal resections was 12 days.[3] For the entire group of 90 patients subjected to resection and end-to-end anastomosis, postoperative hospitalization was only 11 days, while several patients insisted on leaving the hospital as early as the sixth postoperative day.

Comment

The late master of colon surgery, Dr. T. E. Jones, had developed the technical aspect of the combined abdominoperineal resection to such perfection that the operation was practically aseptic and required, in his hands, no special preparation of the bowel. In resections of lesions in the left colon or transverse colon he employed the obstructive resection. Hence there was no indication for preparing the bowel with sulfonamides or antibiotics, and the mortality rate of colon surgery was so low that he once performed 161 consecutive combined abdominoperineal resections for carcinoma without a death.

Despite this extraordinary record there are certain disadvantages to this

method of management. Pathologic studies indicate that carcinomas located above the reflection of the peritoneum rarely metastasize downward[4,5,7] unless the lymphatics above are blocked completely with tumor, in which event it would be unlikely that a cure could be obtained by any method of treatment.[8] Therefore the combined abdominoperineal resection, which removed a perfectly normal rectum along with a cancer of the sigmoid, may be unnecessary for lesions located above the reflection of the peritoneum.[9]

Since exteriorization and obstructive resection is neither a safe nor mechanically sound method of treating lesions just above the reflection of the peritoneum, resection with anastomoses after thorough preparation of the bowel is displacing the other procedures as the preferred treatment. By employing this method the rectum can be saved without jeopardizing the chances of cure in a high percentage of cases which formerly would have been treated by the combined abdominoperineal operation.

The abdominoperineal resection fulfills all requirements of a good operation for cancer and should be employed in its most radical form in the treatment of all lesions below the reflection of the peritoneum. The pull-through modification of this procedure is applicable to carefully selected lesions at this level, but is hazardous and should be employed with caution by those not trained in its fundamental principles.

We have employed variations of the pull-through type of operation in 5 carefully selected cases with low-lying papillary lesions too extensive to fulgurate but not so invasive as to necessitate sacrifice of the sphincter. In 4 of these excellent functional results were obtained, indicating that this procedure has a definite place in the treatment of selected cases.

We should never jeopardize the patients' chances of cure by employing operations which do not allow the surgeon to excise the primary tumor and its zone of metastasis. The operation should be started with this in mind, and then when the tumor and its zone of metastasis are mobilized, the decision may be made as to whether the operation can be completed by re-establishment of continuity or by abdominoperineal resection.

Summary

1. Preoperative preparation of the bowel with sulfonamides and antibiotics, and the prophylactic use of antibiotics after operation have resulted in decreasing mortality and morbidity following operations on the colon.

2. Open end-to-end anastomosis with interrupted sutures has, to a large extent, replaced the operation of obstructive resection and obviated the need of even a temporary colostomy.

3. Resection with anastomosis has supplanted the combined abdominoperineal resection in the treatment of carcinomas located above the reflection of the peritoneal floor.

4. Primary closure of the posterior wounds in the combined abdominoperineal resection has resulted in a striking decrease in the period of convalescence.

5. When it is necessary to establish an end ileostomy and remove the entire colon and rectum for ulcerative colitis or polyposis, the operation appears to be better done in 2 than in 4 stages.

6. Two hundred and seventy-four consecutive resections of the colon and rectum have been performed by the authors without a death.

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ARTIFICIAL KIDNEY

Treatment of Acute and Chronic Uremia

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UNDOUBTEDLY the most important factors in the treatment of both acute and chronic uremia are the proper regulation of diet and maintenance of water and electrolyte balance. Too often the presence of anuria or oliguria encourages the administration of large quantities of fluids in vain attempts to initiate diuresis, resulting in an overload of salt and water and the appearance of symptoms erroneously attributed to uremia.[41]

Where dietary treatment, including rigid control of water and electrolytes, has been ineffective the use of one of the following methods should be considered: 1. artificial kidney, 2. peritoneal dialysis, 3. intestinal dialysis, 4. replacement transfusion. The first of these will be discussed herein.

Principles of the Artificial Kidney

Regardless of the type of artificial kidney used the patient's blood must be rendered incoagulable by the injection of heparin. The blood is then guided along a cellophane membrane on the other side of which is the rinsing fluid. By the process of dialysis a large part of the abnormally retained products of metabolism—urea, uric acid, creatinine, substances giving the xanthoprotein reaction such as phenols,[58] indoxyl, etc. pass from the blood through the cellophane membrane into the rinsing fluid. They become so diluted that return dialysis is negligible. In addition to this process an exchange takes place between the necessary electrolytes of the blood plasma water and those in the rinsing fluid. Hence, if the patient's blood electrolyte pattern is abnormal before treatment, it will tend to be corrected as it approaches the composition of the rinsing fluid inasmuch as the fluid contains normal concentrations of these ions.

Since water passes through the cellophane easily, careful attention must be given the osmotic pressure on the two sides of the membrane. On the inside the blood plasma protein tends to draw water from the rinsing fluid to the blood. This can be prevented by making the rinsing fluid isotonic with the addition of glucose. If so desired it can be made hypertonic and capable of withdrawing fluid from the patient,[56] a maneuver which may be particularly gratifying to patients with pulmonary edema.[16,20,26,39] Figure 1 shows Gamble's diagrams of blood plasma and rinsing fluid. In uremia, as may be seen, the urea accounts for a higher osmotic pressure than normal; however, this can be compensated for by adding glucose to the rinsing fluid. As shown in Figure 1, the total electrolyte content of uremic blood plasma is often lower than in

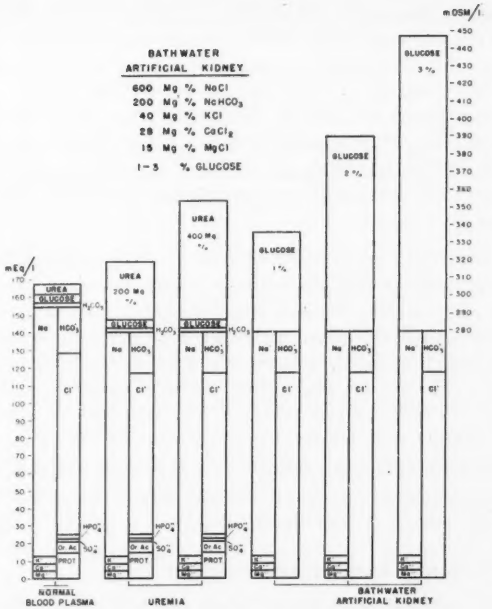

FIG. 1. Gamble diagrams of blood plasma and rinsing fluid. Urea accounts for a considerable rise in osmotic pressure which can be compensated with glucose.

(In this diagram values are expressed mEq/L blood plasma. What really counts however is the value mEq/L blood plasma water.)

normal conditions. A low chloride content cannot always be attributed to vomiting alone. It seems unwise to correct the electrolytes too much as nature may have reasons for lowering them.

Types of Artificial Kidneys

Since Abel, Rowntree and Turner designed the first kidney in 1913, the following types of artificial kidneys have been introduced:

1. Artificial Kidney Employing Dialysis (fig. 2).

The rotating type of artificial kidney which I described in Holland in 1943[21,29] and in Sweden[28] and France[30] in 1944 works purely by dialysis. A thin film of blood moves by gravity through a long cellophane tube wrapped spirally around a rotating drum which is partially immersed in rinsing fluid.

The dialyzing capacity of this kidney in terms of clearance, 100 to 200 cc. per minute as confirmed by others[39] has not been surpassed by any of the devices subsequently developed. While the original model was used by Mac Lean, de Leeuw, van Noorwijk, Palmer and Fishman, and details have been

altered by others (Bywaters and Joekes, Vanatta, Merrill, Kearns,* and Darmady), its main principle of a rotating drum has remained unchanged. This type of kidney has been used successfully on patients in Europe,[11,19,20-31,57,59] Canada,[14,34,46,47] and the United States.[16,37,39] The largest series, 120 cases, has been accumulated by Merrill, Smith, Walters, Callahan and Thorn in Boston. Recently they[39] published the results of 60 dialyses in 43 patients, and through their skillful handling of excellent equipment have confirmed the safety of the method and suggested entirely new possibilities for the use of the artificial kidney.

Vanatta, Muirhead and Grollman who used the artificial kidney in animal studies made an unfavorable preliminary report; however, after effecting some modifications they state: "It may be concluded that dialysis of the blood across a cellophane membrane removes adequately the waste products from the organism, and that death in uremia is a result of the accumulation of such waste products. The results also prove the efficacy of the artificial kidney in replacing known excretory functions."[55] The conclusions of Grollman, Muirhead and Vanatta[17] that bilateral nephrectomy in the dog results in hypertension is, however, not yet confirmed.[33] Reinecke reduced the size of the rotating kidney by winding the cellophane into a coil and subsequently employed it for potassium studies in the dog.[48]

2. Artificial Kidneys Employing Filtration

The purest example of a kidney that works by filtration only is that of Malinow and Korzon.[35] It might be called an artificial glomerulus. Malinow and Korzon discontinued their experiments when they realized the small amount of metabolites that could be removed by filtration as compared with the amount removed by dialysis. The human kidneys need a filtrate of 150 liters per 24 hours to produce 1.5 liters of urine per day. In constructing an artificial kidney that works with filtration, one might have to reinfuse 148.5 liters of fluid per day. The artificial kidneys of Alwall[2] and of Skeggs and Leonards,[50] though designed for dialysis, could be used for filtration if desired.

3. Artificial Kidney Employing Dialysis and Filtration (fig. 3)

With French ingenuity, Derot et al[15] dipped a rat's small intestine in a 10 per cent formol solution for fixation and sterilization. It was then rinsed and one end connected to the radial artery of a patient and the other to a vein. This dialyzing membrane was immersed in rinsing fluid. The older artificial kidneys used collodion tubes or peritoneum; the newer types utilize cellophane tubes or chambers through which blood is forced under pressure while negative pressure is applied through the rinsing fluid. The artificial kidneys designed by Abel, Haas, Necheles, Thalhimer, the dialyzer of Brinkman,[22,31] the kidneys of Alwall, Murray, Slotkin, Sterling, Darmady (laminated type), of Barnard, of Rosenak and MacNeill employ this principle. The most efficient is doubtless

*This type of kidney is manufactured by Allis-Chalmers Manufacturing Company, Milwaukee, Wisconsin.

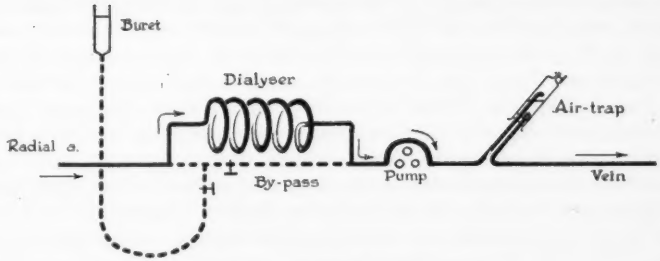

FIG. 2. Blood flows freely from the radial artery to the cellophane membrane where further movement is accomplished by rotation of the drum. The blood in the cellophane tubing is not under pressure. Either pump or the force of gravity returns the blood to the vein. There is practically no filtrating pressure.

the Skeggs' and Leonards' model in which cellophane sheets are compressed between rubber plates; blood and rinsing fluid flow through grooves in the rubber on opposite sides of the cellophane. The dialyzing unit in the "serial counter-flow type of artificial kidney" described by Lowsley and Kirwin in the Urological Society, 1950, used plastic instead of rubber, but is essentially similar to Skeggs' and Leonards' first model (Science 1948).[50] These authors[51] have in the meantime developed a newer, better artificial kidney wherein the blood is retained between sheets of cellophane without coming in contact with the rubber or plastic walls. The kidney designed by Bodo van Garrelts in Stockholm deserves mention as it is little known although its principle is excellent; a large sized cellophane tube is wound together with a long strip of wire mesh into a stationary coil.

I have so far treated a dozen patients with a new type of stationary artificial kidney (fig. 4) designed in collaboration with de Groot, in which cellophane tubing is compressed between specially grooved plastic plates. Our purpose was to compare the clinical results of the stationary and the rotating artificial kidneys.

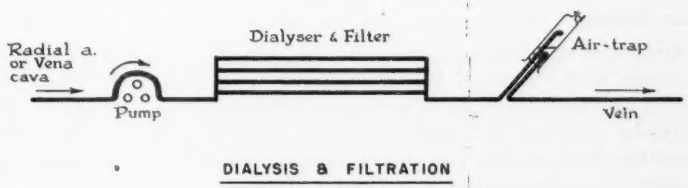

FIG. 3. Blood is forced into the apparatus either by arterial blood pressure or by a pump or both. The blood in the apparatus is under pressure varying from 260 to 20 mm. Hg. In addition, suction may be applied to the rinsing fluid which increases the filtration pressure.

It seems of little importance to me which type of artificial kidney is used although some investigators tend to discredit models other than their own.

Use of the artificial kidneys listed in Section 3 (Artificial Kidney Employing Dialysis and Filtration) necessitates consideration of the water and electrolytes lost by filtration. While apparently simple, these electrolyte and fluid problems may account for clinical disaster. Leonards,[33] for example, suspected that the dehydration and demineralization due to filtration may have accounted for the death of some of the dogs used in his earlier experiments. He now gives a slow infusion of sterile rinsing fluid to compensate for this loss—in his hands a safe procedure. Alwall compensates the colloid osmotic pressure of the blood with filtration. Some authors, however, ignore this problem.

4. Artificial Kidney Employing Exchange Resins

Although promising, this type of kidney is still in its formative stages. The artificial kidney designed by Muirhead and Reid[40] consists of a resin base composed of nine parts cation exchange resin and one part of anion exchange resin. Retention products are absorbed by these substances.

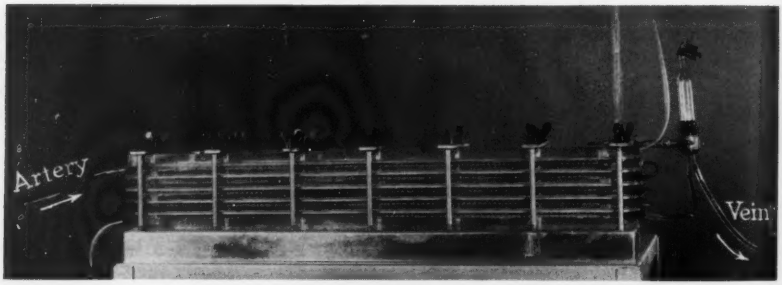

FIG. 4. One dialyzing unit of a stationary type of artificial kidney. Cellophane tubing is compressed between grooved plastic plates. The blood circulates through the cellophane tubing by artificial pressure. No pump is required. The rinsing fluid flows in counter flow either by gravity or propelled by a pump.

Clinical Experience with the Artificial Kidney

Acute Uremia

At present no statistics indicate that the life of a patient may be saved by the action of the artificial kidney (Snapper[52]) because of the comparatively few and heterogenous types so far treated. Muirhead[41] has sought to compare the results observed in 2 patients having mercury poisoning. However, any comparison is debatable. The anuria is usually relieved after 10 days, occasionally after 4 or after 16 days, but sometimes never.

I do not and never did claim that I ever saved a patient with the artificial kidney although many of my patients have now recovered from severe uremia. In judging the possibilities of the artificial kidney we have learned more from

unfavorable cases with protracted courses. For instance, Joekes treated a patient twice with an artificial kidney but discontinued treatment when a diagnosis of renal cortical necrosis became evident after 20 days of anuria. Death did not occur until 8 days later. Alwall, when writing "On the Artificial Kidney, V", had a patient in fair condition who had glomerulonephritis and complete anuria for 30 days. One of my patients, aged 37, died from pneumonia 74 days after the onset of almost complete renal cortical necrosis. She had been given the Borst forced high caloric diet, had been treated twice with the artificial kidney and twice with peritoneal dialysis. With further experience in this field we may prolong life indefinitely. It is obvious that death from acute uremia should be extremely rare. There is no reason to be content with a mortality rate of 15 per cent, claimed by Muirhead,[40] for so-called conservative treatment.

The first dramatic improvement in a patient's clinical condition, followed by complete recovery, was seen in Holland in 1945. A woman of 67 had a cholecystitis with hepatorenal syndrome and anuria of 7 to 10 days' duration. The blood urea was 400 mg. and potassium 55 mg. per hundred ml. She was almost comatose, snored constantly, but answered (usually incorrectly) when shouted at. After treatment with the artificial kidney the blood urea was reduced to 120 mg. and the serum potassium to 19 mg. Although she had not produced any urine, the following day she was completely clear of mind and made reasonable plans for the future. While it is not possible to say whether the clinical improvement was due to the removal of retention products or to the correction of water and electrolyte balance, it was probably due partly to both. The patient recovered completely.

As examples of the treatment of acute uremia with the artificial kidney, histories of 2 cases with mercury poisoning are presented. Other cases which have been treated with equal success include patients with acute glomerulonephritis, lower nephronnephrosis due to sulfonamides and unknown agents.

Case Reports

Case 1. A 26-year-old man swallowed 10 Gm. of bichloride of mercury. Two days later BAL was available and was given in large amounts. The blood urea rapidly rose not withstanding a forced high caloric, low protein diet. The patient was completely anuric and had a temperature of 38 C. Penicillin was prescribed. On the eighth day after taking the bichloride of mercury, the blood urea was 337 mg. per hundred ml. Serum chloride was 525 mg. per hundred ml. (calculated as NaCl) and potassium was 20. On this day we saw the patient and decided that delay might be more dangerous than dialysis. In 6 hours 40 liters of blood flowed through the cellophane tubing; 83 Gm. of urea was removed. Blood urea fell to 154 mg. per hundred ml. After dialysis his general condition was good and no undesirable reactions occurred. His blood urea rose again; however, from the twelfth day his kidney function improved and by the twenty-first day after taking the bichloride of mercury the blood urea was normal.

Case 2. The history of a second patient with mercury poisoning is shown in Figure 5.

Chronic Uremia

The majority of the 24 patients treated by Alwall had chronic nephritis,

polycystic kidney or chronic pyelonephritis.[3] Many of those patients have been benefited by the dialysis. The Boston group of investigators consider the artificial kidney a valuable adjunct in the treatment of severe chronic uremia.[39] In our own experience dialysis has been extremely helpful in chronic uremia. The clinical condition of the patient may be improved so that he is able to take a high caloric diet. It is admitted that the psychosomatic factor plays an important role, but the patient may be in urea balance for many months after the dialysis.

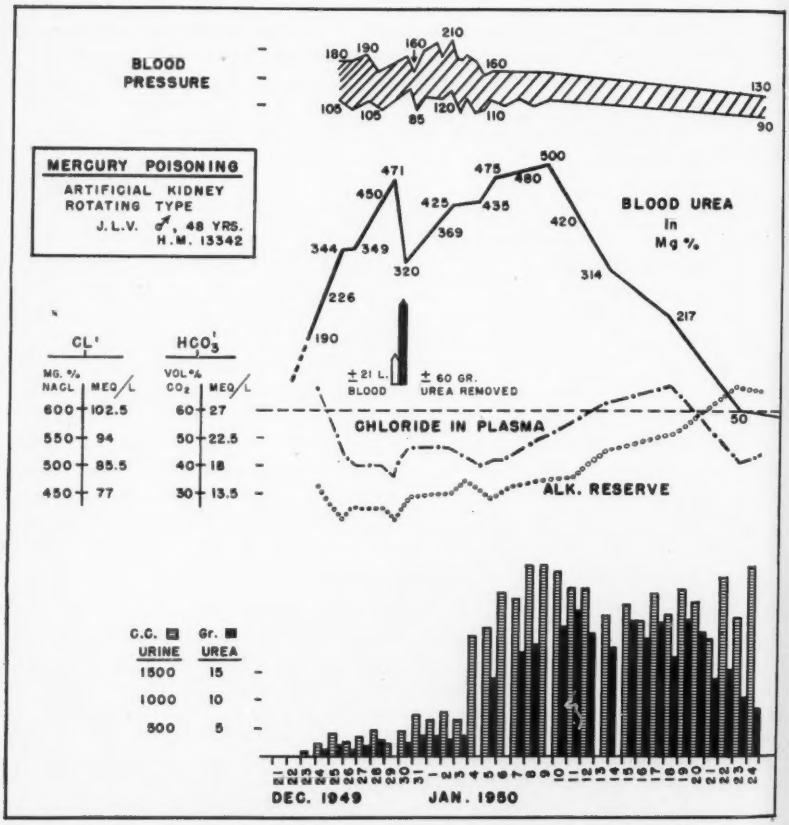

FIG. 5. Graph of a patient with mercury poisoning treated with the artificial kidney, rotating type. Rapid rise in blood urea was due to toxic protein destruction. The forced high caloric diet met with considerable interference due to mercurial colitis accompanied by meteorism and ascites. When the blood urea had risen to 471 mg. per hundred ml. the patient's condition appeared ominous. After dialysis the blood urea rose again to an even higher level, but 14 days after onset of anuria diuresis increased and the patient did not appear unusually ill. He was discharged on the thirty-fourth day with normal blood urea.

Case 3. A college teacher of 27 years (fig. 6) was reported to have had chronic nephritis with albuminuria for 10 years; edema and hypertension for at least 2 years. In addition, there was a history of renal calculi and a deformed left pelvis. He came to the Research Division of the Cleveland Clinic on July 10, 1950, in the last stage of the disease, with rapidly declining urinary output. He was restless and cyanotic, had definite pulmonary edema, a gallop rhythm and pleuritis. His blood pressure was 180/120. To save time a venesection was done. The next morning he was treated with 2 units of our new stationary type of artificial kidney. However, before the beginning of treatment he had a severe convulsion. Three subsequent convulsions occurred during treatment and the patient was comatose during the procedure. One hundred and eighteen grams of urea was removed. The patient's blood urea was reduced from 420 to 147 mg. per hundred ml. Alkali reserve was improved from 14 to 32 volume per cent. Plasma chloride and sodium were purposely reduced. Twenty-four hours later he was greatly improved. His edema had practically disappeared; no gallop rhythm could be heard. His blood pressure was 150/110. However, he now presented symptoms of pulmonary disease. The fine rales of pulmonary edema had disappeared but he showed signs of bronchopneumonia with pleural and pleuropericardial frictions. As his blood urea rose again he was given a second treatment with the artificial kidney on July 15. The same cannulas in the vein and artery were used. The patient was given 250 mg. of sodium amytal and slept during treatment. Not the slightest undesirable reaction was noticed. One hundred and four grams of urea was removed. The blood urea fell from 294 to 84 mg. per hundred ml. The serum potassium was lowered from 7.4 to 4.5 mEq/L. Physical improvement was evident during the next 2 days. The lungs cleared completely; he was clear of mind and resumed his interest in life. The patient's appetite was good and he took his high caloric diet in addition to a normal breakfast; he was ambulatory although still shaky on his feet. His diuresis, however, did not improve. We hoped to treat him with dialysis through an isolated intestinal loop to give him at least a chance to survive but his family refused.

Observations During Treatment with the Artificial Kidney

Removal of retention products with the artificial kidney requires no further discussion. This program was established as early as 1912 by Abel, Rowntree and Turner. In general, there is good correlation between the clinical improvement and chemical changes; however, in my experience, maximum improvement may not be evident for 24 hours following treatment. Furthermore, for reasons not evident dramatic clinical improvement may be noted which is out of proportion to the chemical changes.[39]

Electrolytes

After protracted dialysis the concentration of the electrolytes of the patient's blood plasma water approaches the concentration of these substances in the bath water. At present I use a composition of rinsing fluid which contains less sodium than that used by most investigators, with the exception of Palmer.[46]

NaCl	500 to 600 mg. per hundred ml.
$NaHCO_3$	200
KCl	40
$CaCl_2$	28
$MgCl_2$	10
Glucose	1000 to 3000

The regulation of the electrolytes might be called the tubular function of the artificial kidney. Hence **hyperchloremia** (e. g. from 750 to 660 in 1 case) or **hypochloremia** (e. g. from 462 to 528 in another case) can be corrected. A low NaCl may be adjusted while at the same time the total volume of the extracellular fluid may be reduced[39] by adding more glucose to the rinsing fluid.[56] In the patient with hypertension and convulsions previously discussed (case 3), we purposely reduced the serum **sodium** from 139 to 117 mEq/L.

The **high serum potassium** of the woman aged 67 was reduced from 55 to 21 mg. per hundred ml. Wener and de Leeuw[60] observed similar changes and the Boston investigators[39] currently report 5 cases in which they suggest that the artificial kidney may have been life-saving through the control of

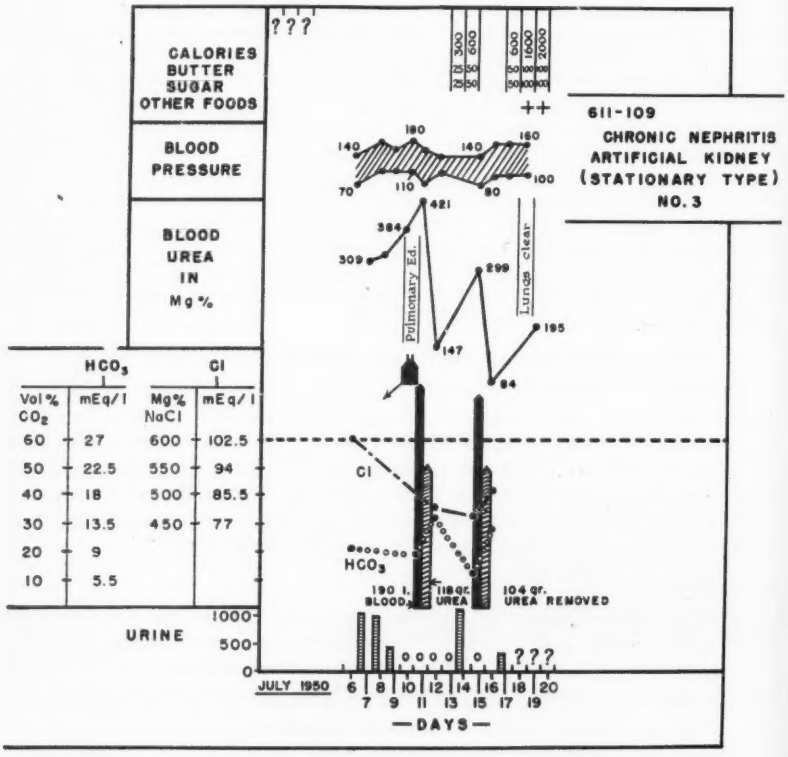

FIG. 6. Patient in terminal stage of chronic nephritis. Uremic condition improved, convulsions ceased, pulmonary edema disappeared, and congestive heart failure subsided after two treatments with the stationary type of artificial kidney. On discharge he resumed a high caloric diet. We cannot estimate how long urea balance may be maintained with the remaining fraction of kidney function.

hyperpotassemia. Reinecke[48] removed 1 to 2 Gm. of potassium from normal dogs by dialysis and found that this could be compensated although the serum potassium would drop, e. g. from 16 to 11.5 mg. per hundred ml. One of Vanatta's[55] experimental dogs developed a low serum potassium (it was quoted as 0.1 mEq/L after the dialysis but had this value been correct the dog probably would not have survived). If serum potassium levels are not measured repeatedly during dialysis it is dangerous to omit the potassium from the rinsing fluid because of the possibility of inducing hypopotassemia.[27]

Calcium may be kept in solution in the rinsing fluid in the presence of $NaHCO_3$ if a pH of approximately 7.4[26,39] is maintained or if the solution is kept in a cool tank and heated just before it is allowed to flow through the artificial kidney. If no calcium is added to the rinsing fluid, calcium gluconate must be given intravenously in order to replace that lost into the bath.

Acidosis may be corrected by dialysis since acids that are retained in uremia are removed. Furthermore, $NaHCO_3$ passes through the cellophane membrane into the blood. If the patient's alkali reserve is especially low it may be wise to give extra $NaHCO_3$ intravenously. Alkalosis can be corrected since the concentration of $NaHCO_3$ of 200 mg. per cent in the rinsing fluid corresponds to an alkali reserve of 53 volume per cent. Blood levels in excess of this amount will loose the ions to the rinsing fluid.

Morphologic changes and hemolysis in the blood during dialysis have been carefully studied by de Leeuw,[13] using the unmodified, unimproved rotating kidney. Figure 6 demonstrates coating of the cellophane with granulocytes. If leukopenia occurs it is corrected within a few hours after dialysis. Hemolysis, which may be evident in dogs, can be avoided in human beings[26] even when the original rotating kidney is used with its original pump, when there is a fair flow of blood. However, the yellowish color of uremic plasma often becomes more intense. No increases in bilirubin values have been evident in such cases; nor were they observed by Merrill and his co-workers.[39]

Earlier in our investigation we observed some hemorrhages due to overdosages of heparin; in the same period Bywaters and Joekes[11] lost a patient from a subdural hematoma. The cerebral petechia in elderly people treated with the artificial kidney at Mount Sinai in New York[16] may also be attributed to excess of heparin. However, since plastic tubing can be used in place of rubber[38] and since all glassware can be coated with dry film[38] or DC* 1107 and less heparin used, such hazards may be avoided. One hundred and fifty to 300 mg. of heparin should be sufficient for one treatment in adults, unless an artificial kidney is utilized with a relatively small clearance which requires a long time for the dialysis. Heparin is instantly neutralized by intravenous injection of protamine.

A so-called toxicity of the cellophane tubes in dog experiments is described by Vanatta, Muirhead and Grollman.[55] Leonards and Skeggs observed the same reaction when using sheets of cellophane. It apparently is of little importance in humans when the cellophane is boiled and rinsed as indi-

Supplied by Dow Corning, Midland, Michigan.

cated.[26,38] Should it become a problem, however, the material can be detoxicified by boiling for a period of 12 hours.[33]

Effects on Arterial Blood Pressure

Transient arterial hypertension was noted by the Boston group in most cases where there was sufficient flow of blood through the kidney.[39] Although I have observed it on occasion, removal of 200 or 300 ml. of blood from the circulation usually has been sufficient to reduce it. In my experience, vasoconstriction may also occur in experiments with the artificial heart. This may be due to the manipulation of blood outside of the body. Further investigation will be necessary to determine whether a lowering of the sodium of the rinsing fluid will reduce the occurrence of this pressure effect.

Indications for Treatment with the Artificial Kidney

Patients with anuria are treated along conservative lines for as long as possible. A patient, however, who has been overtreated with water, salt, diathermy, splanchnic blocks and decapsulation, may be in such condition that immediate treatment with the artificial kidney is imperative. In any patient critically ill with acute or chronic uremia, whatever the cause, dialysis may be attempted. Should dialysis be tried as a last resort in a moribund patient, there is little hope of recovery. In experienced hands, however, treatment with the artificial kidney appears to impose extremely little risk.

There is some logic in the concept that the artificial kidney may be used, not as a last resort when other methods of treatment fail, but as an effective adjunct to more conservative methods of therapy.[39]

Congestive heart failure with pulmonary edema may constitute an additional indication for prompt dialysis in the presence of uremia. The blood necessary to fill the artificial kidney will act as a venesection and the removal of fluid with hypertonic glucose solution into the rinsing fluid will, in many cases, greatly improve pulmonary edema. I can confirm[25] completely the observations of the Boston investigators[39] on this point.

Summary

There are three types of artificial kidneys. 1. Purely dialyzing (Kolff rotating type). 2. Purely filtrating (Malinow and Korzon). 3. Dialyzing and filtrating (all other types).

Vivo dialysis can replace all known excretory functions of the kidney. Moreover it can regulate the electrolyte pattern of the blood plasma water inasmuch as this approaches the composition of the rinsing fluid.

Clinical improvement has been convincing in cases of acute or chronic uremia. In experienced hands treatment with the artificial kidney imposes little risk. It may be an effective adjunct to other methods of treatment. Congestive heart failure in the presence of uremia may be an additional reason for prompt dialysis.

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CHRONIC URTICARIA AND ANGIONEUROTIC EDEMA

Statistical Analysis of 159 Cases

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ONE hundred and fifty-nine cases of chronic urticaria and angioneurotic edema have been observed at the Cleveland Clinic during the 2 year period 1947 to 1948.

Seventy-eight cases were treated in 1947 and 81 during the following year. The over-all incidence of these syndromes as compared to all new admissions to the Clinic was 0.25 per cent.

Urticaria and angioneurotic edema are generally considered as part of the same process occurring in different sites in the skin. This view is supported by the evidence presented in Table 1 which shows that more than half of our patients had both hives and angioneurotic edema.

As shown in Table 2, sex was not a significant factor in the incidence of urticaria. However, angioneurotic edema alone occurred much more frequently in men.

In 102 of the cases in this series the approximate date of onset of the original symptoms was known but we were unable to demonstrate any significant seasonal incidence. This conclusion is not consistent with certain other opinions expressed in the current literature.

Many possible causes have been proposed, and as shown in Table 3, most of our cases have more than one probable etiologic factor. A tabulation of the incidence of the various responsible factors in this series is presented in Table 4.

Of the 26 per cent showing evidence of some focus of infection, 11 patients had tonsillitis, 8 prostatitis, 5 epidermophytosis, 4 sinusitis, 4 evidence of gallbladder abnormality, 14 dental caries, 2 intestinal parasites, and 2 bronchiectasis.

External contactants responsible in 3.2 per cent of the cases studied were shampoo, cosmetics, wool, and shaving cream. In 15.6 per cent of the patients physical agents constituted an etiologic factor. There were 14 instances of pressure, 3 of exercise, 10 of heat, and 2 of cold.

Even though 29.7 per cent of the patients were found to have had a history of constipation, in practically none did the duration of the constipation coincide with that of the urticaria. However, there was suggestive evidence that some correlation existed between the taking of laxatives for the constipation and the urticarial lesions.

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Table 1

	Cases	Per Cent
Hives and angioneurotic edema (ANE)	92	57.8
Hives only	48	30.4
ANE only	19	12.0

Table 2

	Men	Per Cent	Women	Per Cent
Total cases	77	48.4	82	51.6
ANE only	14	....	5	....
Urticaria only	21	....	27	....

Table 3

	Cases	Per Cent
No etiologic factors	15	9.6
One etiologic factor	50	32.2
More than 1 etiologic factor (2 to 6)	90	58.1

Table 4

Etiologic Factors	Per Cent
Focus of infection	26
Suspected food factors	14.4
Possible drug factors	28.8
Possible inhalation factors	7.3
External contactant factors	3.2
Physical agent factors	15.6
History of constipation	29.7
Psychogenic factors	63.5
Endocrine factors	7.1

Table 5

Abnormal Laboratory Tests

Test	No. Cases Tested	Abnormal	Per Cent
Hemotologic			
a. anemic	156	6	3.8
b. eosinophiles	92	11	12.0
c. leukocytosis	156	15	9.6
Urinalysis	148	14	9.5
Blood sugar	150	3	2.0
Serology	152	1	0.6
Stool examination	52	4	....
Gastric analysis	31	6	(low gastric acid)
Basal metabolic rates	16	7	(5 above—2 below) normal

The abnormal laboratory observations are tabulated in Table 5. No known laboratory tests are consistently positive in this condition; even the incidence of eosinophilia is remarkably low. Thus in only 11 out of 92 cases was there any increase (over 4 per cent), these cases varying from 5 to 12 per cent with an average of 7.2 per cent. Besides those tabulated in Table 5, other laboratory tests were made and roentgenograms taken as follows:

Roentgenograms: 57 chests, 24 gallbladder dye, 25 kidney, ureter and bladder, 17 plain gallbladder, 19 upper gastrointestinal, 14 colon, 16 sinuses, 4 skull, 4 urograms, 2 lumbar spine, and 1 each of the cervical spine, shoulder, dorsal spine, knees, and left ankle. There were 6 electrocardiograms, 3 bromsulfalein tests, 3 blood uric acid determinations, 3 blood urea nitrogen determinations, 3 serum calcium determinations, 3 spinal fluid examinations, and 1 urobilinogen determination.

No significant abnormal observations resulted from these tests except for 2 cases of polyps in the paranasal sinuses, 2 cases of sinusitis, and 2 cases of diverticulosis.

Sixty-eight different diseases were diagnosed in this series. However none appeared to be associated with urticaria or angioneurotic edema in significant numbers with the exceptions of chronic allergic rhinitis, psychoneurosis, perennial bronchial asthma, and possibly obesity (table 6).

In no one type of employment did urticaria occur more frequently than in any other.

Of the 55 patients skin-tested for allergies, there were 54 instances of significant reactions to various allergens. (The high incidence of positive skin tests may be explained by the fact that only those patients suspected of having definite allergic conditions are tested. In the absence of symptomatic clues such as cases in which focal infection, drug sensitivity and obvious nervous factors have been excluded, such tests are indicated.) Fifty-two manifested definite reactions to foods; 12 out of 50 showed positive reactions to pollens, and in 54 out of 55 there were pronounced reactions to inhalants, epidermals, molds or bacteria. In addition to those tested in the Clinic, there were 14 other patients who had had previous skin tests elsewhere, 10 of whom showed positive reactions.

We were able to follow 99 of these cases for at least 12½ months. Our longest follow-up was 38¾ months, with an average of slightly more than 23 months. Forty-one patients obtained relief and have remained symptom-free; 27 were improved; 31 were not benefited or have experienced return of the symptoms after original relief (table 7). It must be remembered in evaluating the success of therapy that practically all of the patients in this series had been referred to the Clinic after one or more unsuccessful attempts at treatment elsewhere.

Of the 41 "cures" (table 8), 5 responded and remained improved after the use of antihistaminics alone. Three obtained relief after the use of antihistaminics and other therapy. Out of the 99 cases, 84 had used one or more antihistaminics and 65 of these (77.4 per cent) had experienced at least temporary relief as a result. Therapeutically it is important to note that even

Table 6

	Cases
Chronic allergic rhinitis	41
Various psychoneuroses	33
Perennial bronchial asthma	24
Obesity	14

Table 7

	No. Cases	Per Cent
Cured	41	41.4
Improved	27	27.3
Not helped or relapsed	31	31.3

Table 8

"Cures"

	Only Therapy	Other Associated Therapy
Antihistaminics	5	3
Stock bacteria vaccine	5	4
Other allergenic vaccines	3	3
Avoidance of drugs	5	..
Elimination diets	4	5
Reassurance or removal of neurogenic factors	5	..

though one type of antihistaminic does not work, the administration of others often produces relief. It is essential to realize that failure to respond to these drugs may be due to insufficient dosage. These concepts have been demonstrated in our studies.

A nonspecific therapy commonly used in the Clinic consists of a stock bacterial vaccine containing B. coli, Streptococcus faecalis, B. proteus, Salmonella paratyphi, and S. schottmulleri. In the 99 patients adequately followed, this vaccine was prescribed for 29. Of these 9 were cured, and another showed improvement amounting practically to a cure. The latter patient had 2 minor episodes of angioneurotic edema after taking the vaccine.

In all 5 cases "cured" by avoidance of drugs, the offending agent was either a coal tar derivative or a compound containing phenophthalein. In 5 other cases the patients were aware that various drugs caused hives but had experienced urticaria from other factors as well.

In 1 patient the symptoms persisted until a noninfected cyst was removed from the root of an incisor tooth. One case was "cured" by a cholecystectomy for chronic cholecystitis and 1 by removal of hemorrhoids in which no signs of infection had been evident. In 6 patients treated with oral hydrochloric acid no improvement was noted. Calcium was given to 7 patients either orally or intravenously; in 1 the hives disappeared after 4 months of this therapy. One patient treated with calcium reported some cessation of itching. Of 11

other patients who had had previous calcium therapy, 5 experienced partial temporary relief.

Summary and Conclusions

1. A series of 159 cases of chronic urticaria and angioneurotic edema is reviewed and the observations presented.

2. Chronic urticaria and angioneurotic edema are symptom complexes in which multiple etiologic factors have been thought responsible but no common etiologic denominator demonstrated.

3. While numerous therapeutic agents have proved successful in urticaria and angioneurotic edema, no single therapy has been found beneficial in all cases.

THE USE OF BANTHINE IN THE TREATMENT OF DUODENAL ULCER

A Preliminary Report

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THE treatment of duodenal ulcer and its complications was reviewed recently by one of us (Collins[1]). Eighty-five per cent of our patients obtain relief on the treatment outlined and do not require surgery. The remaining 15 per cent recently have been subjected to vagotomy and gastroenterostomy. Because of this small group demonstrating intractable ulcers, and because of the inconvenience of hourly feedings and medication (which interferes, frequently, with the patient's livelihood), we are interested in any new preparation that serves to relieve pain, heal the ulcer, and eliminate the necessity for surgery.

Longino, Grimson et al[2] reported that Banthine*, an anticholinergic drug, caused prolonged depression of gastrointestinal motility and usually reduction in volume and acidity of secretions from the stomach. Banthine may serve the purpose of a "medical vagotomy." Such treatment for peptic ulcer is not new. Belladonna and atropine derivatives have been used for a long time as adjuncts in the treatment of peptic ulcer. Belladonna and atropine frequently cause severe side effects, however, such as dryness of the mouth and blurring of vision, which make them impractical in the reduction of gastric acidity. Grimson et al[3] have reported the beneficial use of Banthine in 100 patients having duodenal ulcer. Because the drug appears to be effective in reducing gastric acidity without inducing distressing complications, we became interested in its application for duodenal ulcers which had not responded to conventional therapy.

Inasmuch as the results have been unusually satisfactory, we present this preliminary report on our experience with Banthine.

Results

Since January 1950 we have administered Banthine (methantheline bromide) for at least 2 months to 30 of our patients with duodenal ulcer. This is a sufficient period of time in which to determine the patient's response to the medication. The drug, generally, was given only to ulcer patients who had experienced recurrence of the ulcer or some other complication. We preferred to prescribe Banthine in instances where ulcer craters existed, so that some objective evidence concerning the effect might be elicited. Progress roentgen

**We are indebted to Dr. Irwin C. Winter of G. D. Searle and Company for generously supplying Banthine for clinical purposes.*

examinations were obtained within 4 to 8 weeks; patients having come from some distance were unable to obtain these roentgenograms.

Symptomatic Effect of Banthine in Duodenal Ulcer Patients

The majority of the 30 patients given this medication had been troubled with ulcer symptoms for many years (table 1). Three had experienced perforations and 6 hemorrhages; surgery had been considered in most of the patients because of night distress, symptoms of penetration, and lack of response to the prescribed therapy. The symptoms had subsided on the usual ulcer program, but the crater was still evident in 5 patients on roentgenologic examination.

Of the remaining 25 who demonstrated symptoms of active ulcer, only 1 patient exhibited intolerance to the drug. Two patients obtained no relief in 10 and 15 days respectively; surgery was required in 1 patient. Only partial relief was obtained in 3 who required intermediate feedings or antacids in addition to Banthine. Nineteen patients obtained definite and immediate relief with Banthine medication. These 19 did not require intermediate meals or antacids after having been on this therapy for a short time.

Typical comments were: "Most comfortable 6 weeks of my life"; "Now eating things I have avoided for 30 years—even take an occasional drink"; "Much better than I have been for years." These statements are similar to those made by patients who have undergone bilateral vagotomy and gastroenterostomy.

In 19 of the 25 patients with relatively intractable ulcers not improved by previous therapy, the symptoms disappeared usually in 1 to 4 days following introduction of Banthine. This drug has, apparently, an extremely useful function in the treatment of duodenal ulcers, and is capable of performing "medical vagotomies" when prescribed in appropriate dosages. Many patients, because of personal reactions and job requirements, are unable to adhere to the modified Sippy program of ulcer therapy. The most dynamic, active and tense patient may take Banthine 4 times a day without difficulty.

Roentgenologic Observations

In the group of 30 cases of duodenal ulcer observed, 3 patients did not continue the medication; therefore progress roentgenograms were not obtained. Since many of our patients live in communities at a great distance from the Clinic, progress x-rays were not available in an additional 9. In 18 patients, stomach roentgenograms were obtained 4 to 8 weeks after Banthine therapy was initiated. Because we attempted to restrict the use of this drug to patients with active ulcer craters for the purpose of obtaining objective evidence, each of the 18 demonstrated this defect on initial examination. Progress examinations of 17 of these patients revealed disappearance of the ulcer craters; in the remaining case a questionable crater was reported. We have not observed such remarkable results with any other type of ulcer therapy.

Table 1

EFFECT OF BANTHINE ON PATIENTS WITH DUODENAL ULCER

No.	Age	Sex	Duration	Complications	Effect of Banthine	X-Ray Findings	
						Before Banthine	After Banthine
1.	42	M	12 years	Perforation, 1946; recurrences	Immediate relief	Ulcer crater	Not available
2.	50	M	26 years	Repeated recurrences	No relief (15 days)	Ulcer crater	
3.	54	M	2 months	Symptoms responded to usual ulcer program but crater persisted	None	Ulcer crater	No crater
4.	45	M	20 years	Repeated recurrences; surgery advised	Complete relief	Marked deformity; crater	No crater
5.	65	M	25 years	Responded to usual ulcer program but crater remained	None	Crater	No crater
6.	39	M	20 years	Repeated recurrence	Prompt relief	Crater	No crater
7.	41	M	24 years	Responded to usual ulcer program but crater persisted	None	Crater	No crater
8.	32	M	15 years	Repeated recurrence	Prompt relief	Crater and deformity	No crater; less deformity
9.	39	M	13 years	Repeated recurrence	Prompt relief	Crater and deformity	No crater, less deformity
10.	35	M	17 years	Repeated recurrence when not on ulcer program	Prompt relief	Crater and deformity	No crater
11.	54	M	15 years	Responded to usual ulcer program but crater persisted	None	Crater	No crater, some deformity
12.	48	M	5 years	Usual ulcer symptoms; hemorrhage, 1949	Immediate relief	Crater and deformity	Not available
13.	41	M	12 years	Hemorrhage, 1939, 1950; symptoms disappeared on usual ulcer program but crater remained	None	Crater	No crater, minimal deformity
14.	28	M	6 months	Usual ulcer symptoms	Immediate relief	Ulcer crater	No crater, minimal deformity
15.	36	M	13 years	Repeated recurrence: hemorrhage, 1950	Prompt relief	Questionable crater and deformity	Not available

Table 1 (continued)

No.	Age	Sex	Duration	Complications	Effect of Banthine	X-Ray Findings	
						Before Banthine	After Banthine
16.	35	M	12 years	Repeated recurrence	Prompt relief	Deformity and crater	No crater, less deformity
17.	58	M	20 years	Night distress, back pain; had not responded to usual ulcer program	Immediate relief	Deformity and crater	Normal bulb
18.	42	F	5 years	Symptoms disappeared but crater remained	Did not tolerate drug		
19.	35	M	7 years	Repeated recurrence of ulcer	Immediate relief	Deformity and crater	Not available
20.	46	M	6 months	Usual ulcer symptoms	Prompt relief	Deformity and crater	Not available
21.	39	M	9 months	Considerable night distress	Prompt relief	Deformity and crater	No crater, little deformity
22.	38	M	9 months	Pain in back, vomiting	Prompt relief	Marked deformity, large crater	Deformity, questionable crater
23.	45	M	25 years	Considerable night distress	No relief in 10 days; Banthine discontinued	Deformity; no crater	
24.	23	M	2 years	Usual ulcer symptoms; hemorrhage	Immediate relief	Ulcer deformity	Not available
25.	34	M	12 years	Usual ulcer symptoms, 1 hemorrhage and 1 perforation; symptoms persisted despite usual treatment	Prompt relief	Deformity and crater	Not available
26.	50	F	8 years	Repeated recurrence	Partial relief	Deformity and crater	Not available
27.	52	M	20 years	Repeated recurrence, 3 hemorrhages	Prompt relief	Deformity and crater	Not available
28.	34	M	2 years	Repeated recurrence	Immediate relief	Deformity and crater	Not available
29.	37	M	10 years	Repeated recurrence, 1 perforation	Partial relief	Marked deformity	Not available
30.	44	F	20 years	Repeated recurrence; surgery advised	Immediate relief	Ulcer crater	No crater

Use of Banthine in Other Conditions

The effect of this drug in several other gastrointestinal conditions is presented in Table 2.

Levin, Kirsner and Palmer,[4] and Levin et al[5] have shown that gastric ulcers do not have the continued noctural acid secretion or the high acidity typical of duodenal ulcers; consequently vagal stimulation probably has little to do with the pathogenesis of gastric ulcers in contrast to duodenal ulcers. The two conditions appear to be two separate diseases. On an experimental basis, Banthine was prescribed to 2 patients with gastric ulcers. One of these was unable to tolerate the drug. The other patient was given Banthine for a period of almost 3 months. At the conclusion of this therapy the ulcer of the latter patient was as large as at the onset of treatment, and gastric resection was necessary. Banthine had no effect upon this benign gastric ulcer.

Inasmuch as marginal ulcers have responded favorably to surgical vagotomy, this is recognized as the treatment of choice. One patient who had a long ulcer history, accompanied by recurrences and 12 hemorrhages for which a gastroenterostomy was performed in 1941, followed by a vagotomy 8 years later, was placed on Banthine therapy for a marginal ulcer. The ulcer pain disappeared completely, and on progress roentgen examination 6 weeks later the crater could no longer be visualized. The patient, however, objected to the excessive dryness produced by even one 50 mg. tablet taken daily, and discontinued the use of the drug.

Factors of nervous tension and the psychosomatic aspects of ulcerative colitis have been given recent extensive study. Although bilateral vagotomies have been performed for the treatment of ulcerative colitis, we do not believe the procedure to be physiologic for the reason that the vagus nerve, at the most, innervates only the right colon, whereas the disease begins in the rectum and extends proximally. Because Banthine produces some effect on each division of the parasympathetic system, 1 patient with ulcerative colitis was placed on this therapy. The patient underwent a relapse while on Banthine medication.

Two patients who demonstrated syndromes of severe hyperacidity simulating peptic ulcer, but whose roentgenologic examinations were negative, were treated with Banthine. In both instances night pain ceased, and each patient believed this medication to have been of more positive value than the usual ulcer program. Another who manifested the irritable colon syndrome, with belching and epigastric fullness following meals, obtained no relief from Banthine. A patient having a severely irritable bladder condition, associated with an acute Hunner's ulcer, showed a pronounced decrease in urinary symptoms after Banthine therapy.

Many other conditions exist, such as irritable colon, functional bladder disturbances, dysmenorrhea and ulcerative colitis, in which definite nervous factors are present, which might conceivably respond to Banthine medication. However, the results in these other conditions have not been outstanding, although too few patients have been given Banthine to warrant definite conclusions.

Table 2
USE OF BANTHINE IN THE THERAPY OF OTHER CONDITIONS

1. **Gastric ulcer**					
43	M	6 years	Recurrent symptoms	Gastric ulcer	Continued to have pain; ulcer crater, remained same size despite 3 months of Banthine therapy
58	M	10 years	Repeated recurrences	Gastric ulcer	Did not tolerate Banthine
2. **Marginal ulcer**					
42	M	20 years	Repeated recurrences; 12 hemorrhages; gastroenterostomy 1941; vagotomy 1949	Marginal ulcer	Pain disappeared and crater disappeared; stopped drug after 1 month because of dryness
3. **Ulcerative colitis**					
44	M		Developed relapse of acute toxic ulcerative colitis while on Banthine		
4. **Hyperacidity syndrome**					
39	M	15 years	Severe ulcer-like symptoms, night distress; partially relieved by ulcer program	Repeated x-rays negative	No night pain while on Banthine; continued on intermediate feedings; more relief than with other medication
35	M	11 years	Ulcer-like symptoms with night distress	Repeated x-rays negative	Excellent result; more relief than on ulcer program or any other therapy
5. **Irritable colon**					
53	M	7 years	Belching and fullness after meals	Negative	No relief with Banthine

Toxic Effects of Banthine

Pharmacologically, the action of Banthine is anticholinergic and provides autonomic ganglion blockade, principally effecting the parasympathetic division. Side reactions of the drug are usually mild. In only 3 of the 37 were complications severe enough to warrant cessation of the therapy. One of these patients had a duodenal ulcer, another a gastric ulcer, and a third a marginal ulcer. Excessive dryness of the mouth and disturbances of vision necessitated discontinuance of Banthine medication.

The full dose of 8 tablets was given daily to 28 patients. In 15 no appreciable side reactions developed. Thirteen manifested accompanying complications with symptoms of severe dryness evident in 11, slow urinary stream in 6, impaired visual focus in 5, and constipation, hoarseness and impotence in 1. Because of these reactions the dosage was reduced in 6 of the 28 patients; 9 were placed on a smaller dose consisting of either 4 or 6 tablets a day. Of

these latter, 2 had visual disturbances and 2 dryness of the mouth. These reactions were more severe during the first week of treatment, and usually subsided thereafter. No apparently extreme toxic symptoms occurred in any of our patients.

Because of occasional difficulty in urination, this medication is contraindicated in a patient with prostatic hypertrophy. A 67-year-old man recently admitted to the hospital on the service of Dr. C. C. Higgins illustrates this point clearly. This patient gave a history of nocturia, slow urinary stream and a decrease in the size of the stream, "rolling" abdominal discomfort and diarrhea of 3 years' duration. He was given Banthine by a local druggist without the advice of a physician. The following day he developed acute urinary retention. Cystoscopic examination was negative except for a large prostate. He was treated by the use of an indwelling catheter and subsequent prostatectomy. This medication should not be given to patients with prostatic enlargement and should not be dispensed except on the advice of a physician.

Whether long-continued use of this drug will result in intolerance to the medication or severe toxic reactions has not, as yet, been determined, inasmuch as none of our patients have undergone the therapy for a significant interval.

Summary

A new anticholinergic drug, Banthine, was prescribed for 30 patients with duodenal ulcers. Out of the group of 25 having active symptoms, 19 obtained definite and immediate symptomatic relief. Seventeen of 18 patients originally demonstrating ulcer craters showed healing of the crater on progress examination.

The majority of patients under observation tolerated the full dose of 100 mg. every 6 hours without undue complications. Out of a total of 37, 3 discontinued the drug because of distressing reactions which included dryness of the mouth, visual difficulties, slowness of urination and, rarely, constipation and hoarseness. The drug should not be given to patients with enlarged prostates or bladder neck obstructions. One patient with an enlarged prostate developed acute urinary retention after one day's medication with Banthine.

Seven patients presenting other gastrointestinal problems were given the medication. This group is not sufficiently large to warrant any conclusions; preliminary results were disappointing in this small group, however. Empirically, the drug may be of value in such conditions as irritable colon, the syndrome of hyperacidity, ulcerative colitis, functional bladder difficulties, and dysmenorrhea.

This report is entirely preliminary. Further studies on gastric acidity and nocturnal secretion, as well as the employment of a similar-appearing placebo tablet (for control), are indicated. It will be interesting to determine whether a small dose of the drug, such as 50 mg. 4 times a day, may be effective in preventing recurrences of duodenal ulcer.

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CARCINOMA OF THE CERVIX

Trends in Treatment

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DESPITE numerous technical and clinical advances in the methods of treatment of carcinoma of the cervix, 65 to 75 per cent of patients with this disease die within 5 years. There are many factors responsible for this alarming death rate, the most common of which is the failure of patients to seek medical advice early enough. In Miller's[1] series there was a 7 months' delay from the onset of symptoms before medical attention was sought. Another factor is that physicians frequently minimize the importance of symptoms and do not recognize the signs of cancer of the uterus.

In considering the treatment of uterine cervical cancer, it is customary to classify cases according to the League of Nations Stages.

Stage I

The carcinoma is strictly confined to the cervix.

Stage II

Parametrium—the carcinoma infiltrates the parametrium on one or both sides but has not invaded the pelvic wall.

Vagina—the carcinoma infiltrates the vagina but does not involve its lower third.

Corpus—endocervical carcinoma which has spread to the corpus.

Stage III

Parametrium—the carcinomatous infiltration of the parametrium on one or both sides has invaded the pelvic wall. On rectal examination no cancer-free space is found between the tumor and pelvic wall.

Vagina—the carcinoma involves the lower third of the vagina. Isolated carcinomatous metastases are palpable on the pelvic wall (irrespective of the extent of the primary cervical growth).

Stage IV

Bladder—the carcinoma involves the bladder as determined by the presence of a vesicovaginal fistula.

Rectum—the carcinoma involves the rectum.

Distant spread—the carcinoma has spread outside the true pelvis (below the vaginal inlet, above pelvic brim, distant metastases).

This clinical classification has considerably more bearing on the prognosis and therapeutic regimen than the pathologic grading of the tumor.

Eighty per cent[2] of patients reporting will have extension beyond the cervix when first examined. The number of patients surviving 5 years or more is proportional to the anatomic extent of the lesion. The general average of 5 year survivals is approximately 80 per cent in Stage I; 52 per cent in Stage II; 23 per cent in Stage III, and 3 per cent in Stage IV.[3]

In studying preinvasive carcinoma of the cervix, Pund et al[4] believe that most carcinomas have been present for a period of 2 to 6 years before causing symptoms. They base this on the fact that the average age of patients with preinvasive carcinoma is 36.6 years and for those with grossly detectable cancer 44.2 years.

General Consideration of Treatment

The treatment of carcinoma of the cervix with radium was popularized in the United States in 1912 by Kelly and Burnam.[5] Previously the method of treatment had been principally surgical. Wertheim and Bonney,[6] in Europe, had perfected their operative technic for selected cases and were obtaining a fair number of cures. However, they had a large operative mortality (12 to 20 per cent), and there was a long period of convalescence. In addition, the operation was technically difficult.

After its introduction, the use of radium became so popular that it soon replaced surgery. The reasons are obvious; there was ease of application, low primary mortality and minimal morbidity. However, after a period of experimentation, it was found that, in many cases apparently cured with radium, the carcinoma recurred in a year or more with parametrial involvement.

In the early 1930s much work was done on radium dosage. Arneson[7] studied the dosage delivered by radium when applied by various methods. He concluded that a tandem in the cervix and uterus, plus colpostats in the lateral fornices, gave the best distribution without over-irradiating normal tissues. He found that the dosage delivered decreased greatly toward the lateral wall of the pelvis. It was also observed that it would be impossible to bring the dosage up to a cancerocidal level in the parametrium by means of radium alone.

Since the local lesion in the cervix can be controlled readily by radium, it is the involvement of the parametria and pelvic lymph nodes which determines the outcome. Fricke[8] points out that the nodes are located several centimeters from the cervix. The nodes first involved are the primary nodes: the hypogastric, the obturator nodes at the bifurcation of the common iliac vessels, the external iliac chain, and the ureteral nodes. The secondary nodes, which are usually involved later, are those in relation to the common iliac vessels, the middle and lateral sacrals, and the aortic chain.[9]

Because of the limitations of radium dosage, external roentgen therapy was used to supplement the radiation, particularly to the parametria. A constant effort has been made, since this time, to administer as large a dose of roentgen rays and radium to the tumor and its extentions as is feasible and still preserve the normal uninvaded surrounding structures.

It was determined, from experience, that squamous cell carcinoma could be controlled by 7000 to 10,000 r. The tolerance of the other normal tissues in the area must be considered in any plan of radiation therapy. The limit of tolerance of the bladder and rectum must be below 10,000 r and any amount over 7000 r to the femora endangers their vitality. The therapist must consider all of these factors in his estimation of dosage and its methods of application for each individual case.

Radiation Therapy

We believe that, wherever possible, treatment should be begun with preliminary external roentgen therapy followed by radium therapy. Roentgen therapy given first has five advantages:[3] (1) Neoplastic cells which may be disseminated by manipulation are devitalized; (2) lymphatics are partially sealed; (3) ever present local infection is diminished; (4) anatomic relationships, which are distorted by the cancer, are re-established, and (5) there is an increase of 5 to 10 per cent in the 5 year survival rate when roentgen therapy precedes radium application, particularly in advanced cases.

This initial roentgen therapy is given through direct portals, one anterior and one posterior. In most cases we attempt to give 1000 r to the parametria and cervix. Larger doses may cause atresia of the vagina or cervical canal, which complicates the application of radium.

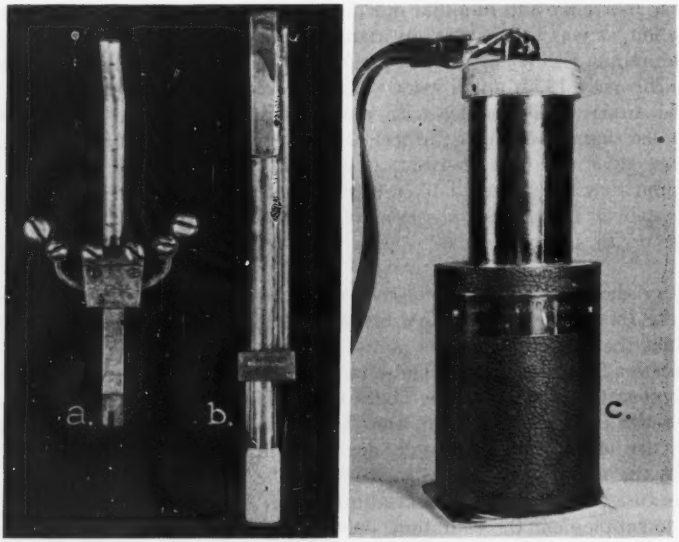

FIG. 1. (a) Ernst applicator in opened position. (b) Handle used for inserting and opening applicator. (c) Carrier for storing and transporting applicator. Personnel are protected by lead collar about carrier.

Following this preliminary roentgen therapy, patients are immediately hospitalized and radium is applied. For this purpose we have found the applicator designed by Ernst[10] of St. Louis to be extremely useful in many cases (fig. 1). It consists of an intra-uterine section containing three 10 mg. sources of radium, and expanding side arms for extension into the lateral fornices. Each side arm contains three 10 mg. radium sources. The total filtration of each is equivalent to 1.0 mm. of platinum. The applicator is inserted closed and the side arms are expanded after insertion. This not only delivers the radium laterally as far as possible, but it also serves to hold the applicator in position. A gauze roll impregnated with barium sulfate suspension is used to pack the bladder and rectum as far from the radiation sources as possible. Offensive odors are also minimized by use of the barium which also acts as an astringent. Anterior-posterior and lateral roentgenograms are made immediately following the insertion to check on the location of the sources. This procedure makes it possible to adjust the applicator, if necessary, before too much time has elapsed.

The advantages of this applicator are many: it is quickly and easily positioned and removed, thereby reducing the exposure of the therapist; the relative positions of the several radium sources remain constant and can be duplicated; the spacing of the radium tends to give a more adequate and homogeneous distribution of the radiation; the dosage to the bladder and rectum is minimal because of 2 mm. of lead incorporated in the ends of the vaginal sources and by the fact that the sources do not tend to slip.

The applicator is left in place for 48 hours and a second 48 hour application is made in 7 days. This fractionation permits giving a much larger dose than can be given with safety at one sitting. Using this method, 8640 mg. hours are administered which deliver 8500 gamma r to Point A; 3000 gamma r to Point B (fig. 2). These are the optimum doses advocated by Tod.[11]

Occasionally it is impossible to insert the complete applicator because of anatomic distortion of the structures. Under such circumstances one or more of the sources may be removed from either the uterine stem or from the vaginal portion of the applicator.

In cases that cannot be treated with the Ernst applicator, or in those cases which present unusual problems, some modification of the Manchester method may be employed (fig. 3). This technic was popularized by Tod and Meredith.[12] It consists of an intra-uterine tandem of radium sources and, in addition, 2 vaginal ovoids which are placed as far laterally into the fornices as possible, and held apart by a spacer. From the anatomic shape of the paracervical and parametrial tissues they planned the arrangement of the radium sources to give isodose curves which produced a cancerocidal dose at Point A. The radium is divided into units of 5 mg., 6.66 mg. and 10 mg. In the intrauterine tandem they place the following number of units, 2, 2, 1 with the single unit at the cervix. The ovoids for the fornices are of 3 sizes, large, medium and small, and contain 5, 4 or 3 units respectively.

Dosage by means of this system is calculated in gamma r and depends on the size of the unit employed, i. e. whether 5 mg., 6.66 mg. or 10 mg. Whether

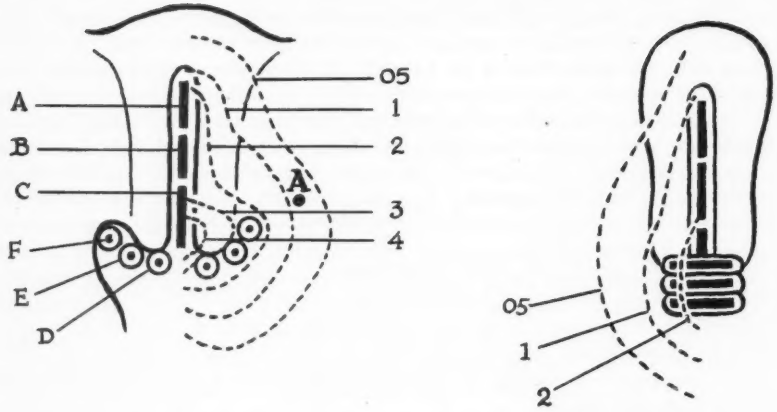

FIG. 2. Isodose curves in gamma r per mg. hour with fully loaded Ernst applicator.

one uses a small ovoid or a large one does not appreciably affect the dosage, provided the largest that can be accommodated is employed. With 5 mg. units 1000 gamma r will be delivered at Point A in 24 hrs.; 1333 r with 6.66 mg. sources and 2000 gamma r with 10 mg. sources. In this country Harris and Silverstone[13] and Hunt[14] have used a modification of this method with excellent results.

In addition to the methods of intracavitary radium therapy described, there are variations known as the Paris and Stockholm technics. The Manchester method is a modification of the Paris technic. The Paris method differs from the Stockholm technic in that it is a more or less continuous application of radium, and the vaginal and intra-uterine applications are not administered simultaneously but consecutively. With the Stockholm method 3 large doses are administered at weekly or biweekly intervals and the sources are more heavily filtered with lead than in the Paris technic.

Because of the failure of centrally placed radium to give a lethal tumor dose at the lateral pelvic wall, Pitts and Waterman[15,16] in 1926 initiated interstitial radium therapy with long needles for cancer of the cervix. Their technic consisted of inserting a 20 mg. radium tube into the cervical and uterine canal; 2 needles of 3 mg. content are inserted into each lateral fornix and 4 to 6 needles of 2 mg. radium content into each anterior and posterior fornix. The needles are left in place for 168 hours.

Corscaden et al[17] have devised a somewhat different approach to the method of parametrial radium needle implantation. Their technic consists of an intra-uterine tandem plus a stockade of 8 radium needles containing 2 mg. each inserted into the cervix. On each side, 1½ cm. lateral to the stockade, 2 needles of the same strength as the cervical needles are inserted. One and one-half cm. lateral to those needles, or 4.5 cm. from the cervical canal, 5 needles 6 cm. long and containing 4.8 mg. of radium are inserted against the

lateral pelvic wall. All sources are left in place for 120 hours. After operation, stereoscopic roentgenograms of the pelvis are made and by means of the precision stereoscope the dosage in gamma r calculated. With this method mentioned, 11,000 gamma r are delivered to the cervix, 14,400 to the paracervical region, and 10,000 gamma r to the lateral pelvic wall. This indicates that the dosage throughout the entire potentially diseased tissue is homogenous, balanced and adequate. The authors have used it in Stage III lesions and are encouraged by the immediate beneficial results.

Radioactive cobalt 60 needles are being used instead of radium needles and seem to offer certain advantages. They are thinner and cause less trauma than the conventional needles. The gamma radiation is more homogeneous than that from radium.

Roentgen Therapy

Because the intensity of radiation from radium sources obeys the inverse square law, there is a rapid diminution in the parametria laterally. It was recognized early that those cases which were not controlled by radium were ones in which the disease had spread beyond the cervix. Unfortunately, this was true in 80 per cent. As can be seen by the technics described there is a decrease to 3000 gamma r at the lateral pelvic wall. This amount is insufficient to control cancer.

In order to build up the dosage in the lateral portion of the parametria, interstitial radium needles or roentgen therapy are used. We believe that all carcinomas of the cervix should receive roentgen therapy in addition to radium, except in early Stage I lesions. The roentgen therapy should be started before radium insertion, as previously stated. Immediately after the radium treatment another course of roentgen therapy is prescribed. This is given through split anterior and posterior 15 by 20 cm. fields with a strip of lead 5 cm. wide in the center of the fields dividing them in two. A depth dose of 3000 to 3500 r is given to the parametria.

The reason for the split field is to protect the cervix, rectum, and bladder from further radiation, which in addition to the dosage from radium, might exceed the tissue tolerance of these structures. Lateral pelvic fields are not employed because we do not believe they add significantly to the dose, and fractures of the femoral neck may result from over-irradiation. Perineal fields are not advocated because severe skin reactions are produced and there is little increase in the depth dose.

Transvaginal administration of roentgen rays has come into popular usage in the last 10 years due to the efforts of Merritt,[18] Erskine,[19] Wasson,[20] and Sante[21]. This is accomplished by directing the rays through a cone inserted in the vagina. This type of therapy offers the theoretical advantages of a uniform field, adequate dosage, and directional control for selected cases.

A 3 cm. cone is about the largest which can be inserted into the vagina without excessive discomfort, and 30 cm. is the shortest focal skin distance that is practicable. Every effort should be made to divert the beam away from the

hollow of the sacrum and from the rectum. In some patients it may be possible to use a small cone and angle the beam into the right and left parametria. Nolan and Stanbro[22] believe that 3 vaginal fields of application offer the best distribution to the cervix and portions of the parametria. They advocate administering 5000 r to each field in increments of 300 to 500 r daily.

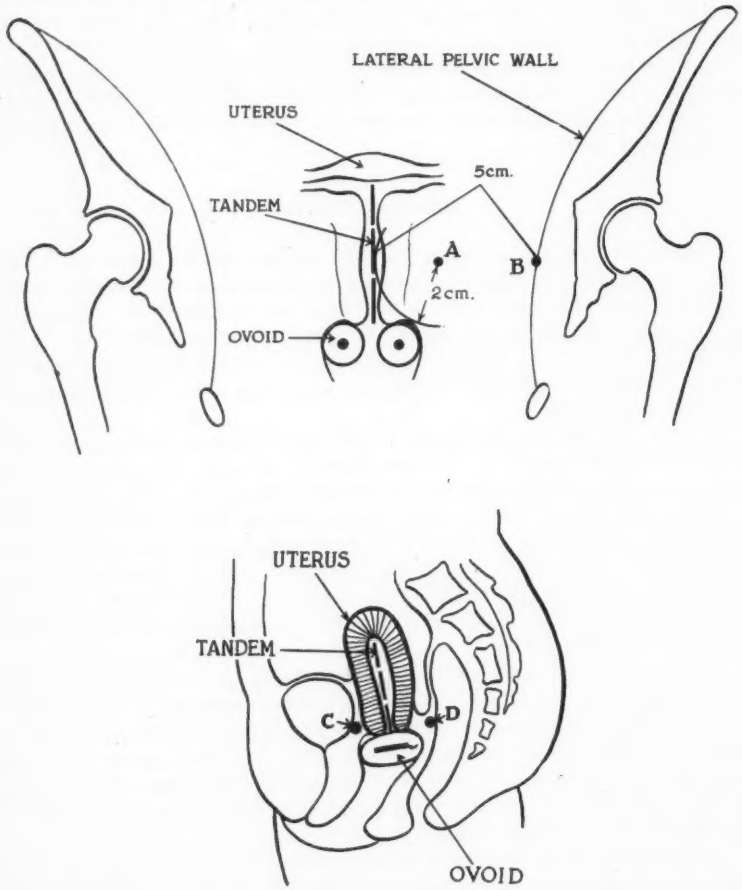

Fig. 3. Diagram of pelvis illustrating position of intra-uterine tandem and vaginal ovoids employed in Manchester system. Point A is located in paracervical triangle where uterine artery crosses ureter. This point is 2 cm. lateral to central axis of uterus and 2 cm. above lateral fornix of vagina. Point B, located in lateral parametrium 5 cm. from midline, is location of principle lymph nodes involved in carcinomas of cervix. Points C and D are bladder and rectal wall, respectively.

In some clinics this type of therapy has replaced radium, particularly for early lesions. External roentgen therapy can be used to supplement the parametrial dosage. It is particularly adaptable to carcinoma of the cervical stump and to patients who have had previous radium therapy with recurrences.

Surgical Treatment

While radiation therapy remains the treatment of choice for most invasive carcinomas of the cervix, there has been revival of interest in the surgical approach in Stage I and early Stage II cases. Since 1939 Meigs[23] has performed the Wertheim type of operation plus pelvic lymphadenectomy in these early cases. He believes that radiation therapy has reached a plateau and that something further must be done to improve results. From his observations at operation he believes that the pelvic nodes constitute the obstruction to the cure of some cases of carcinoma of the cervix.[23] He found metastases in 18 per cent of nodes in cases considered clinically to be Stage I, and 28 per cent in Stage II. Both Meigs[23] and Taussig[24] doubt the ability of radiation therapy to sterilize squamous cell carcinoma in lymph nodes. They cite the failure of roentgen therapy to control metastases in peripheral nodes, such as metastases in cervical nodes from carcinoma of the tongue. Taussig[24] advocated pelvic lymphadenectomy in Stage II cases either before or after radiation therapy.

Bonney operated on 63 per cent of the patients presenting themselves and had an operative mortality of 14 per cent. The over-all 5 year survival rate was 41 per cent. Read,[25] on the other hand, operates on only 14 per cent of his patients. Meigs recommends that the patient be under 50 years of age and thin. The tumor may invade the entire cervix and extend not more than 1 cm. into the vaginal wall. The cervix must be movable.

Results of Treatments

The results of treatment are based on the number of patients living and well at the end of 5 years. A large series of statistics has been compiled by Swanberg.[26] He reported on 1796 cases from 1933 to 1938, treated by several different radiation technics. The findings are listed in the Table.

	Stage I	Stage II	Stage III	Stage IV	Total
Number of patients	208	550	738	300	1796
Relative 5 year cure rate .	56.2	40.7	26.4	5.7	32.2

Meredith[27] using the Manchester technic of irradiation, has been improving his results constantly by giving larger doses with radium in Stages I and II and by adding roentgen therapy in Stages III and IV. He averages between 8000 and 9500 r at Point A. He believes that higher doses do not improve the results. Tod,[11] using these higher doses, reports a 3 year survival rate of 83 per cent in Stage I, 57 per cent in Stage II and 38 per cent in Stage III.

Meigs,[23] by carefully selecting his cases for radical surgery, had a 3 year survival rate of 77.7 per cent. Due to his strict rules for selection, it is possible that his 5 year survival rate will not differ greatly from his 3 year rate.

Arneson[28] compared the results of surgical and radiation therapy for carcinoma of the cervix in two large series of cases treated in different clinics. Bonney's surgically treated patients were compared with those given radiation therapy by Pitts and Waterman. Bonney treated 63 per cent of the patients presenting themselves and Pitts and Waterman treated 76 per cent in Schmitz Stages, I, II and III. The 5 year survival rate in Bonney's cases was 40 per cent and in Pitts and Waterman's, 76 per cent.

The controversy of surgery versus radiation in the treatment of Stage I and II cases revolves about the inability of radiation to control carcinoma in lymph nodes. Taussig[24] compared results among 70 iliac lymphadenectomies and 118 Stage II patients treated by irradiation alone. While 38.6 per cent of patients with node dissection survived 5 years, the rate was 22.9 per cent for radiation. Morton[29] noted that there was 39.3 per cent involvement of nodes in cases operated upon with no irradiation and only 11.4 per cent in postirradiation cases. Obviously no positive conclusions can be drawn as yet from these figures.

Conclusions

Radiation therapy by the combined use of radium and roentgen rays is still the preferred method of treatment in the majority of cases of carcinoma of the cervix. The trend is toward larger fractionated doses of radium so that undesirable reactions are minimized.

Palliation of advanced cancers may be afforded by the judicious use of roentgen therapy. Radium is contraindicated in patients with severe anemia and cachexia.

Radiation in the form of interstitial parametrial needles appears to offer an excellent method of obtaining satisfactory dosage throughout the involved tissues.

A few expert surgeons have demonstrated that operation is satisfactory in early cases. It would appear that irradiation followed in 2 to 3 months by iliac lymphadenectomy offers, in suitable cases, a concrete means of improving our results and curing patients with involvement of lymph nodes.

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ANNOUNCEMENTS

Dr. John W. King has been appointed to the staff in the Department of Clinical Pathology. Dr. King attended Pennsylvania State College, receiving his B.S. degree from that institution in 1936, and his M.S. degree (bacteriology) in 1937. He attended Yale University from 1938 until 1944, received the degree of Ph.D. in 1941 and M.D. in 1944. After having interned and served a residency at Jefferson Medical College Hospital, Dr. King became assistant professor (later associate professor) of bacteriology and clinical pathology at the College of Medicine of the University of Vermont, 1945 to 1950. During the last two years he also served as clinical pathologist to the Mary Fletcher Hospital. Dr. King was certified by the American Board of Pathology in 1950 in the field of clinical pathology. He is a member of the Chittenden County and Vermont State Medical Societies, the American Society of Clinical Pathologists, and the Society of American Bacteriologists. He has contributed numerous articles to the medical literature.

On August 1, Dr. John A. Hunter was made a member of the permanent staff in the Department of Neuropsychiatry. Dr. Hunter attended Western Reserve University in 1934 and 1935, and received his Bachelor of Arts degree from Johns Hopkins University in 1938. In 1942 he was graduated from Western Reserve School of Medicine following which he served an internship in St. Luke's Hospital, Cleveland. From July, 1943 until August, 1946 he was in the Medical Corps of the United States Army. He then returned to Cleveland and served a year's residency in the Department of Psychiatry at Cleveland City Hospital. Dr. Hunter was a fellow in Neurology at the Cleveland Clinic for three years preceding his appointment to assistant staff on January 1 of this year. He is a member of the Cleveland Academy of Medicine, the Cleveland Society of Neurology and Psychiatry, the American Psychiatric Association, the American Academy of Neurology, and the Cleveland Medical Library Association.

On September 1, Dr. James S. Krieger joined the staff in the Department of Gynecology of the Division of Surgery. Dr. Krieger was graduated from the University of Michigan in 1941 with a B.S. degree and received his M.D. degree from the Medical School of the same university in 1944. He interned at University Hospital, Ann Arbor, and served two subsequent periods of residency there, interrupted by service in the U. S. Army. Immediately preceding his present appointment, Dr. Krieger was an instructor in the Medical School of the University of Michigan.

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